ASsessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) Consortium

Version:

November 2019

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A. INTRODUCTION

A.1. Overview

A.1.1. History of the Increasing Recognition about the Importance of Acute Kidney Injury

Acute kidney injury (AKI) refers to a sudden, unexpected decrease in kidney function. This phenomenon has been best studied among hospitalized patients. It is well known that dialysis-requiring AKI is associated with a high risk (>30%) of short-term mortality.[1, 2] The importance of AKI as a clinical and public health problem is underscored by recent studies showing a rising incidence in the U.S. over the past several decades.[2, 3]

The vast majority of published studies on AKI have focused only on clinical outcomes that occur during the index hospitalization complicated by AKI and have been limited by several methodological challenges. Thus, relatively little is known about long-term clinical outcomes among patients who suffer hospital-acquired AKI, including the risk of development and acceleration of chronic kidney disease (CKD), death, cardiovascular events, and other important patient-centered outcomes. The 2005 American Society of Nephrology Renal Research Report listed as a research priority "increased epidemiologic research in acute kidney injury." The report also listed as one of the "critically important gaps in knowledge" in the field of AKI that "there are no data on long-term outcomes" after an episode of AKI.[1]

To address these knowledge gaps, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) released an RFA (DK-07-009 "*Ancillary Studies in the Natural History of Acute Kidney Injury*") in 2007 to create a multi-center collaboration that would enroll and conduct long-term follow-up in a prospective cohort of participants with and without AKI.

A.1.2. Study Design and General Plan

The **ASsessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) Consortium** has been established and includes Clinical Research Centers (CRCs) led by Kaiser Permanente of Northern California, Yale University, Vanderbilt University, and University of Washington as well as a Data Coordinating Center at The Pennsylvania State University and representatives from NIDDK. The overall goals of ASSESS-AKI are to make significant contributions to the field of AKI in the five following areas:

- Establishing a diverse prospective parallel, matched cohort of adults and children with and without AKI.
- Characterizing the short-term and long-term natural history of AKI based on current serum creatinine-based diagnostic criteria.
- Evaluating the incremental utility of novel blood and urine biomarkers to refine the diagnosis and prognosis of AKI.
- Developing a prognostic risk score that integrates patient characteristics and biomarkers to help inform providers and patients about the risks of adverse events after an episode of AKI.

- Identifying the subset of high-risk patients with AKI who could be targeted for future interventional clinical trials to improve outcomes after an episode of AKI.

The following sections of the ASSESS-AKI Protocol describe in detail the Specific Aims and major hypotheses, study design and recruitment strategies, measurements, statistical considerations, study management, and human subjects considerations.

A.2. Specific Aims and Study Hypotheses

The ASSESS-AKI Consortium will address the following Specific Aims through the initiation and follow-up of a long-term prospective cohort of participants with and without evidence of acute kidney injury (AKI) based on serum creatinine-based criteria:

A.2.1. Primary Aims

Aim 1. To determine whether hospitalized persons who survive an episode of AKI have a greater risk of developing chronic kidney disease or faster progression of pre-existing chronic kidney disease than hospitalized persons without AKI after accounting for pre-existing level of kidney function and potential confounders.

Aim 2. To determine whether hospitalized persons who suffer from an episode of AKI have a higher risk of death, cardiovascular events, and other adverse events after hospital discharge than matched persons who did not suffer AKI during hospitalization, after accounting for pre-existing level of kidney function and potential confounders.

A.2.2. Secondary Aims

Aim 3. To evaluate the incremental value of serial measurements of several different blood and urine biomarkers for predicting short- and long-term clinical outcomes after an episode of AKI currently defined using a serum creatinine-based criteria.

Aim 4. To assess whether severity and type of the AKI episode and the presence of pre-existing chronic kidney disease influence long-term risks of loss of kidney function, death, and cardiovascular events in persons with AKI.

Aim 5. To determine if persons who completely recover kidney function within three months of an episode of AKI have a lower risk of adverse events than those persons with AKI whose recovery is incomplete.

Aim 6. To develop a risk score incorporating demographic features, clinical factors, and/or biomarkers that accurately predicts outcomes after an episode of AKI.

A.3. Rationale for Selecting Specific Aims

The proposed Specific Aims directly support the stated goals of RFA (DK-07-009 "*Ancillary Studies in the Natural History of Acute Kidney Injury*") and will allow ASSESS-AKI to meet the major challenges outlined in *Section A.1*. ASSESS-AKI will implement a cost-effective study design of a matched, parallel cohort design with adequate sample size and power to address the high priority research questions and knowledge gaps in the field of AKI within a geographically and sociodemographically diverse population. Our Specific Aims focus primarily on clinically relevant outcomes, both renal and non-renal, and will also begin to address other outcomes of interest such as selected patient-centered outcomes as well as policy-relevant aspects of resource utilization. In addition, the study design will provide flexibility for better understanding the future role of novel biomarkers in the prognosis and diagnosis of AKI. Finally, this set of Specific Aims and study design will establish a platform to answer current and future questions involving the epidemiology and prognosis of AKI and to provide clinically useful tools for providers and patients.

A.4. Study Hypotheses

Aim 1. To determine whether hospitalized persons who survive an episode of AKI have a greater risk of developing chronic kidney disease or faster progression of pre-existing chronic kidney disease than hospitalized persons without AKI, after accounting for pre-existing level of kidney function and potential confounders.

> *Hypothesis 1a. An episode of AKI independently increases the risk of incident chronic kidney disease in persons without pre-existing chronic kidney disease.*
>
> *Hypothesis 1b. An episode of AKI independently increases the risk of faster progression of chronic kidney disease and development of end-stage renal disease (ESRD) in persons with pre-existing chronic kidney disease.*

Aim 2. To determine whether hospitalized persons who suffer from an episode of AKI have a higher risk of death, cardiovascular events, and other adverse events after hospital discharge than matched persons who did not suffer AKI during hospitalization, after accounting for pre-existing level of kidney function and potential confounders.

> *Hypothesis 2. AKI increases the short- and long-term risks of death from any cause, cardiovascular events, and other adverse outcomes (e.g., poorer cognitive function, quality of life, or functional status) in persons with and without pre-existing chronic kidney disease, even after adjustment for potential confounders.*

Aim 3. To evaluate the incremental value of serial measurements of several different blood and urine biomarkers for predicting short- and long-term clinical outcomes after an episode of AKI currently defined using changes in serum creatinine.

> *Hypothesis 3. Novel serum and/or urine biomarkers can improve the clinical prognosis after an episode of AKI using a serum creatinine-based definition.*

Aim 4. To assess whether severity and type of the AKI episode and the presence of pre-existing chronic kidney disease influence long-term risks of loss of kidney function, death, and cardiovascular events in persons with AKI.

Hypothesis 4. Greater severity of an AKI episode (presumed acute tubular necrosis etiology), and the presence and severity of pre-existing chronic kidney disease raise the risk of adverse outcomes after an episode of AKI.

Aim 5. To determine if persons who completely recover kidney function within three months of an episode of AKI have a lower risk of adverse events than those persons with AKI whose recovery is incomplete.

Hypothesis 5. Persons who have incomplete recovery of kidney function within three months after an episode of AKI have a higher risk of adverse clinical outcomes that is mediated primarily through incident and progressive chronic kidney disease.

Aim 6. To develop a risk score incorporating demographic features, clinical factors, and/or biomarkers that accurately predicts outcomes after an episode of AKI.

Hypothesis 6. A clinically useful and easily implementable risk score can be developed that integrates information on individual characteristics and/or serum/urine biomarkers to provide robust prognostic information for individuals who experience an episode of AKI.

B. BACKGROUND

B.1. Epidemiology of AKI

B.1.1. Incidence of AKI

The incidence of acute kidney injury (AKI) in hospitalized patients varies from 1.9% to 7.2% of hospitalized patients.[2-6] Part of the variability of the incidence relates to heterogeneous definitions of AKI applied in previous studies. However, studies that have examined temporal trends in the incidence of AKI over time using the same definitions over different time periods have demonstrated that the incidence of hospital-based AKI has been increasing significantly over the past several years.[4,7,8] Within a large integrated healthcare delivery system, Hsu and colleagues from Kaiser Permanente of Northern California defined occurrence of AKI during hospitalization based on serum creatinine-based definitions rather than administrative diagnostic codes, indicating that the increased incidence of AKI is true and not due to increased recognition or more aggressive administrative coding.[8]

In patients undergoing cardiac surgery, one of the more common clinical settings for AKI, the incidence of AKI is lowest among those undergoing coronary artery bypass (CABG) alone, followed by valvular surgery, and combined coronary CABG/valvular surgery, which has the highest incidence.[9] The incidence of AKI that requires dialysis increases in parallel with the three types of surgery.

The median length of hospital stay in patients with AKI is approximately seven days.[3,4] The costs associated with uncomplicated AKI (excluding patients in the ICU) result in the third highest median direct hospital costs ($2,600) after acute myocardial infarction and stroke.[10] Other studies have confirmed the high medical costs associated with AKI.[11]

B.1.2. Risk Factors for AKI

Several studies have examined risk factors for the development of AKI. One of the most important risk factors is pre-existing kidney dysfunction. Data from the PICARD Study demonstrated that a third of patients with AKI had stage 4 CKD or worse.[12] A recent study within Kaiser Permanente of Northern California found that 74% of cases of dialysis-requiring AKI occurred among patients with eGFR < 60 ml/min/1.73 m^2 prior to admission.[13] Even after adjustment for other known clinical risk factors for AKI, there was a graded risk between baseline level of eGFR and risk for experiencing dialysis-requiring AKI (**Table 1**). Documented proteinuria, another manifestation of underlying kidney dysfunction, was also independently associated with an increased risk of AKI.

Table 1. Risk Factors for development of dialysis-requiring AKI among hospitalized adults[13]

Risk-factor	Adjusted Odds Ratio† for Dialysis-Requiring AKI (95% Confidence Interval)
Baseline estimated glomerular filtration rate (ml/min/1.73m^2)	
≥ 60	Reference
45-59	1.66 (1.40-1.97)
30-44	4.75 (4.01-5.63)
15-29	20.42 (17.40-23.96)
< 15	47.17 (39.22-56.74)
Diabetes mellitus	1.99 (1.78-2.23)
Diagnosed hypertension	1.55 (1.37-1.76)
Documented proteinuria	2.84 (2.52-3.19)

†Adjusted for hyperbilirubinemia, intensive care unit stay, mechanical ventilation, CABG, other cardiac surgery, percutaneous coronary intervention, and cardiac catheterization including intravenous contrast.

Other notable risk factors for AKI include older age,[8,14,15] other organ dysfunction (cardiac,[14-17] pulmonary,[14,15] liver[14,15,18]), infection,[15] and acidosis.[19]

There are also several risk factors specifically associated with AKI after cardiac surgery (**Table 2**).

Table 2. Risk factors associated with AKI in the setting of cardiac surgery[20,21]

Patient-related	Procedure-Related
Female gender	Length of Cardiopulmonary bypass
Chronic obstructive pulmonary disease	Cross-clamp time
Diabetes	Off-pump vs. on-pump CABG
Peripheral vascular disease	Non-pulsatile flow
Pre-existing kidney dysfunction	Hemolysis
Left ventricular ejection fraction < 35%	Hemodilution
Emergent surgery	
Cardiogenic shock requiring intra-aortic balloon pump	
Left main coronary artery disease	

As is the case for AKI in hospitalized patients, pre-operative kidney function is one of the most important risk factors for the development of AKI. Of note, off-pump CABG is associated with a lower risk of AKI compared with on-pump CABG.

B.1.3. Short-term Mortality after AKI

The short-term risk of death associated with AKI ranges from 20% to 70%.[4,12,22] The mortality associated with AKI varies depending on the clinical setting and associated severity of underlying illnesses, but it can be as high as 60% to 70% in critically ill patients with severe degrees of kidney dysfunction.[22-24] In patients undergoing cardiac surgery, the mortality ranges from 15% to 30%, but it can also be as high as 60% in those who require acute renal replacement therapy.[20,25-27]

Many recent studies have demonstrated that even milder forms of AKI, as manifested by very small increases in serum creatinine, are also associated with a significant increase in mortality in selected

populations.[28] For example, Chertow et al. found that patients with an increase in serum creatinine as little as 0.3 to 0.4 mg/dl had a 70% higher multivariable-adjusted odds of death compared with patients who had smaller or no change in serum creatinine.[11]

Two major challenges in interpreting the results of previous epidemiologic studies of AKI are the lack of a well-defined "baseline" level of kidney function and the fact that several different definitions of AKI have been used which makes it difficult to compare directly risks of death and other outcomes after AKI across different studies. However, as described in the next section (*Section B.2.1*), recent attempts to develop a consensus definition of AKI have been made in order to facilitate standardization across studies of AKI.

B.2. Diagnosis of AKI

B.2.1. RIFLE and AKIN Classification Scheme for AKI

B.2.1.1. *RIFLE Classification Scheme*

As noted above, more than 30 different definitions for AKI have been used in the literature, which has made comparison of the epidemiology and outcomes of AKI across studies very difficult. In 2002, the Acute Dialysis Quality Initiative (ADQI), a collaboration of nephrologists and intensivists, met to address topics relevant to the field of AKI.[29] The first objective was to derive a consensus definition/ classification system for AKI. The committee devised a five-tiered classification scheme related to AKI that was termed "RIFLE" ('Risk', 'Injury', 'Failure', 'Loss' and 'End stage renal disease'), with the first three levels related to the degree of kidney dysfunction followed by two clinical outcomes (Figure 1).[30]

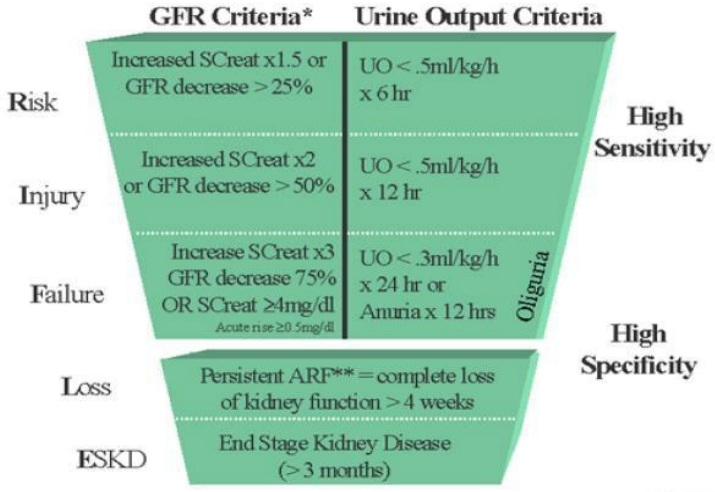


Figure 1. RIFLE Classification Scheme for AKI

Since the proposal of the RIFLE classification scheme in 2004, at least 24 studies that aimed to validate RIFLE have been published, as summarized by a recent systematic review and meta-analysis.[31] These studies have encompassed more than 71,000 patients. Compared with patients who did not appear to have AKI based on RIFLE criteria, there was an observed stepwise increase in the risk of death with the first three levels of AKI per RIFLE: crude mortality in patients without AKI was 6.9% compared with 18.9%,

36.1%, and 46.5% in those with Risk, Injury, and Failure, respectively. The corresponding relative risk for death was 2.4, 4.14, and 6.37, respectively, for the three stages versus non-AKI patients.[31] When stratified by clinical setting, it appeared that AKI carried the greatest relative risk for death in patients that underwent cardiac surgery. It should be noted that urine output criteria were not used in several studies. In addition, it appeared that the urine output criteria, when utilized, were too sensitive, and decreased the discriminatory capacity of the classification system.

B.2.1.2. *AKIN Classification Scheme*

The Acute Kidney Injury Network (AKIN), an international consortium composed of representatives from major critical care and nephrology societies and associations, held its first conference in September 2005. The first priority of this meeting was to create a uniform definition for AKI. After deliberation, the AKIN group endorsed the following definition of AKI (that built upon the already existing RIFLE classification scheme):

An abrupt (within 48 hours) reduction in kidney function currently defined as any of the following:

- *An absolute increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 μmol/l)*
- *A percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline)*
- *A significant reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours).[32]*

The committee also recognized a need for staging of severity of AKI and proposed the following stages:

- *Stage 1: an absolute increase of 0.3 mg/dl or a 50% increase above baseline serum creatinine*
- *Stage 2: a 100% increase above baseline serum creatinine*
- *Stage 3: a 300% increase above baseline serum creatinine or renal replacement therapy (RRT)*

Two recent studies have compared the RIFLE and AKIN criteria for AKI. Bagshaw et al. performed a retrospective study of 120,123 critically ill patients admitted to 57 ICUs in Australia and New Zealand between 2000 and 2005.[33] The investigators did not demonstrate any significant differences in hospital mortality or duration of stay between the two classification systems. A much smaller single-center study of 703 critically ill patients in Portugal demonstrated very similar results, as there were no significant differences in mortality between either of the AKI classification systems.[34] The AKIN definition did; however, appear to improve sensitivity for the diagnosis of AKI.

While the results of these two recent studies indicate that the AKIN classification system is not materially better that the pre-existing RIFLE system, there was similar predictive value for important outcomes, and the sensitivity for AKI appears to be better. Given this, it can be argued that the AKIN classification system can serve as an initial approach for new studies of AKI in order to provide a standard comparison for new classification schemes and for identification of new prognostic factors among uniformly defined populations.

B.2.2. <u>Biomarkers for Diagnosing AKI</u>

Several biomarkers specific for kidney injury have been identified over the past several years. In this section, we briefly review current pre-clinical and clinical data on selected biomarkers that appear to be specific for kidney injury.

B.2.2.1. *Urinary IL-18*

The intracellular cysteine protease, caspase-1, converts the pro-form of the cytokines IL-1β and IL-18 to their active forms.[35,36] As caspase-1 deficient mice were protected against ischemic AKI, IL-1β and IL-18 were investigated as potential mediators of AKI. It was discovered that ischemic AKI causes kidney IL-18 levels to more than double and induces the conversion of the IL-18 precursor to the active form. This conversion is not observed in caspase-1 -/- mice or sham-operated controls. [35,36] Injection of IL-18 neutralizing antiserum before the ischemic insult protects mice against ischemic AKI to a similar degree as seen in the caspase-1 deficient mice. The active form of IL-18 exits the cell and may enter the urine after being activated in proximal tubules. IL-18 was identified via immunohistochemistry in freshly isolated mouse proximal tubules and in tubular lumens of ischemic mouse kidneys. In mice, urinary IL-18 concentration was increased in ischemic AKI compared with sham-operated mice.[35]

Clinical studies have demonstrated that urinary IL-18 levels can assist in the diagnosis and classification of AKI. Persons with acute tubular necrosis have significantly higher median urinary IL-18 concentrations than persons with all other types of renal dysfunction (e.g., CKD, pre-renal azotemia, urinary tract infection).[37] Furthermore, IL-18 has good accuracy for the early diagnosis of AKI.[38,39] The area under the curve (AUC) estimates—one measure of the utility of a diagnostic test—for urinary IL-18 ranged from 0.54 to 0.9 for the early diagnosis of AKI in different studies. [38,39] In three of the studies possessing lower AUCs, urinary IL-18 level demonstrated low sensitivity but high specificity (0.85-0.94).[38-40] The performance of urinary IL-18 also is dependent on the timing of collection in relation to the exposure (e.g., the stressor such as cardiac surgery) and the outcome (development of AKI).[38,39] In summary, urinary IL-18 has performed moderately well for detecting AKI early in four different populations (adults undergoing cardiac surgery, children admitted with critical illness, adults with acute lung injury, and adults receiving kidney transplantation). In addition to its diagnostic potential for AKI, urine IL-18 possesses prognostic value for duration of AKI[39] and is an independent predictor of in-hospital mortality in selected populations.[38]

B.2.2.2. *Urinary NGAL*

Neutrophil gelatinase-associated lipocalin (NGAL) is expressed at very low levels in the kidney, trachea, lungs, stomach, and colon. Its expression is markedly increased in stimulated epithelia. Using cDNA microarray techniques, the NGAL gene was discovered to be upregulated more than 10 fold in the early post-ischemic mouse kidney.[41] Importantly, NGAL is upregulated in the urine very early after both ischemic[42] or nephrotoxic[43] injury in animal models. The role of NGAL in the kidney seems to be two-fold. First, it is renoprotective—exogenous infusion of NGAL significantly ameliorated renal apoptosis and necrosis after ischemia-reperfusion injury in mice.[44] Secondly, NGAL may enhance the recovery phase of AKI by enhancing re-epithelialization.

In children undergoing cardiac surgery[45] and in adults receiving deceased donor kidneys,[46] urinary NGAL concentrations were highly predictive of subsequent clinical diagnosis of AKI (sensitivity 1.0, specificity 0.98, AUC 0.99 at two hours post-surgery in the children and sensitivity 0.9, specificity 0.83, AUC 0.90 in the adults undergoing kidney transplantation). In contrast to these initial highly promising results, subsequent studies in separate populations have not yielded results as robust, with sensitivities and specificities for detecting AKI below 80% in a cohort of adults undergoing cardiac surgery[47] and in a cohort of critically ill children.[48]

B.2.2.3. *Urinary KIM-1*

Kidney injury molecule 1 (KIM-1) is a transmembrane protein that was identified by representational difference analysis of normal and regenerating rat kidneys.[49] KIM-1 expression has been localized to proliferating proximal tubular epithelial cells. KIM-1 is shed into the urine in multiple models of ischemic[49] and nephrotoxic[50] AKI. Of note, it has recently been proposed to the U.S. Food and Drug Administration (FDA) and the European Medicines Evaluation Agency to be included as one of seven new biomarkers for characterizing kidney injury in preclinical animal models for drug safety studies.

A small study in six patients with confirmed ATN confirmed KIM-1 expression via immunohistochemistry on kidney biopsy.[51] The same investigators subsequently examined urinary KIM-1 concentrations in 40 patients.[51] KIM-1 levels were elevated to a much higher degree in patients with ischemic ATN than in patients with contrast nephropathy, other forms of AKI, patients with CKD, or in normal non-AKI participants. In a cohort of adults undergoing CABG, urinary KIM-1 levels were predictive of subsequent AKI (sensitivity 0.74, specificity 0.9, AUC 0.83 at twelve hours post-surgery).[52] The results from these studies suggest that urinary KIM-1 may be useful in identifying ischemic ATN.

B.2.2.4. *Urinary L-FABP*

In experimental models of CKD, free fatty acids bound to albumin play an important role in tubulointerstitial inflammation and progression of kidney disease. Liver fatty acid binding protein (L-FABP) expression is stimulated by cytosolic free fatty acids. Thus, L-FABP has been proposed as a biomarker for CKD.[53] By extension, L-FABP has been proposed as a potential biomarker for AKI and has been shown to be upregulated in a cisplatin-based animal model of AKI.[54] Treatment of such animals with fibrates was renoprotective and associated with a reduction in L-FABP levels in the urine, suggesting that endogenous L-FABP may indeed play a critical role in scavenging free fatty acids after experimental cell injury.[54,55]

Limited clinical data exist on the utility of urinary L-FABP. However, in one study of children undergoing cardiac surgery, urinary L-FABP concentrations were predictive for the subsequent clinical diagnosis of AKI (sensitivity 0.71, specificity 0.68, AUC 0.81 at four hours post-operatively).[56]

B.2.2.5. *Serum Cystatin C*

Cystatin C is a 13 kD cysteine protease inhibitor that has been proposed as a more sensitive marker of glomerular filtration rate than serum creatinine.[57] Rises in serum cystatin C precede changes in serum creatinine by one to two days in AKI, with an AUC of 0.97 and 0.82 at one and two days, respectively.[58]

B.2.2.6. *Plasma IL-6*

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that has been shown in several studies to have predictive value for AKI. In animal models of AKI, interleukin-6 levels rise within two hours of injury, and the kidney may play a role in IL-6 generation as well as clearance.[59] In a population of critically ill patients with severe sepsis, IL-6 levels predicted AKI over the next seven days,[60] even after adjustment. Similarly, in a population of patients with acute lung injury, IL-6 levels predicted AKI over the next 4 days.[61] However, there are limited data on the sensitivity and specificity of IL-6 for the prediction of AKI.

B.3. Acute Complications of AKI

A recent systematic review by investigators at Yale analyzed studies that examined the mortality associated with AKI as defined by very small changes in serum creatinine during hospitalization. The results indicate that among published studies, even very small increases in serum creatinine concentration (i.e., relative increases of 10% to 24% or absolute increases of 0.3 to 0.4 mg/dL) are associated with approximately a twofold higher relative risk for short-term death (RR 1.8 for relative serum creatinine increases and RR 2.3 for absolute serum creatinine increases, respectively) across a broad-spectrum of clinical settings. Furthermore, larger changes in serum creatinine concentration (i.e., relative increase of 25% to 49% or absolute increase of 0.5-0.9 mg/dL) were associated with a threefold to six-fold increase in the risk of short-term death **(**Figures 2 and 3**).**

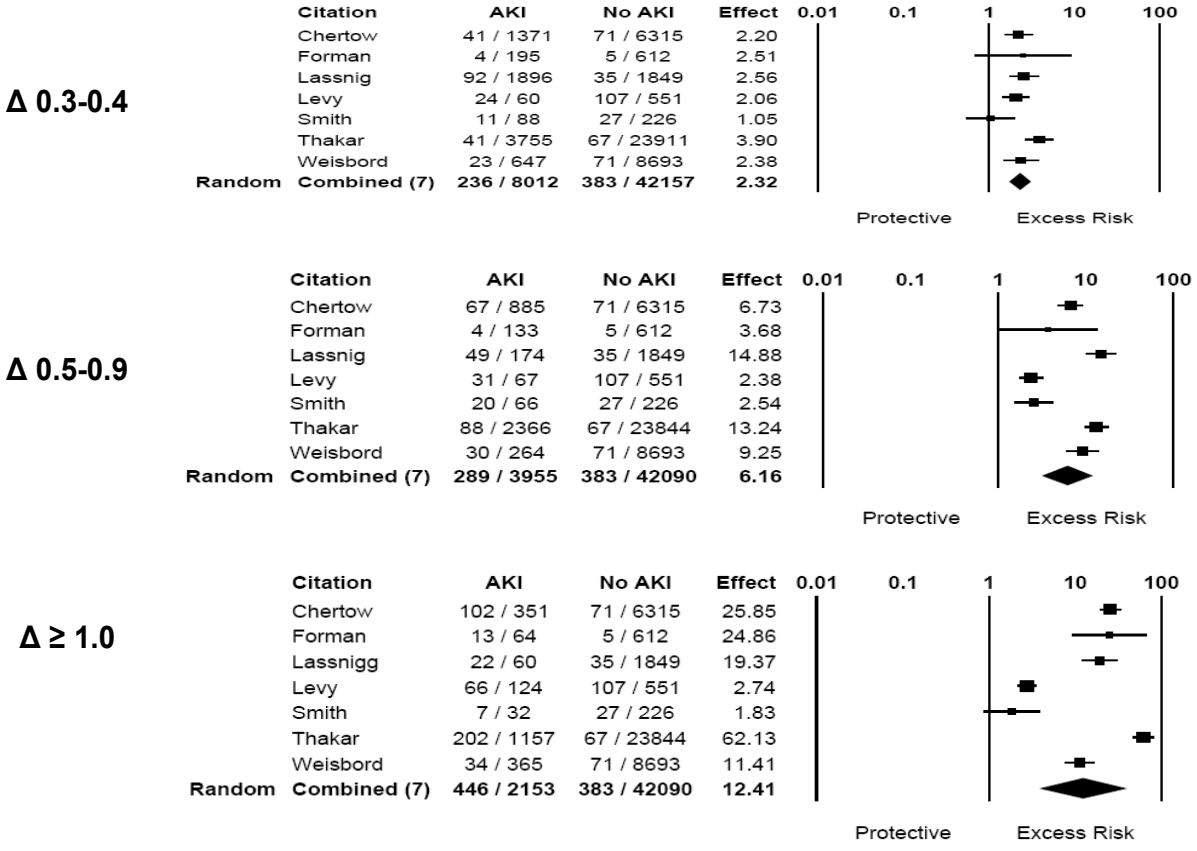


Figure 2. Short-term death associated with AKI (defined by *absolute* increases in serum creatinine, mg/dL)

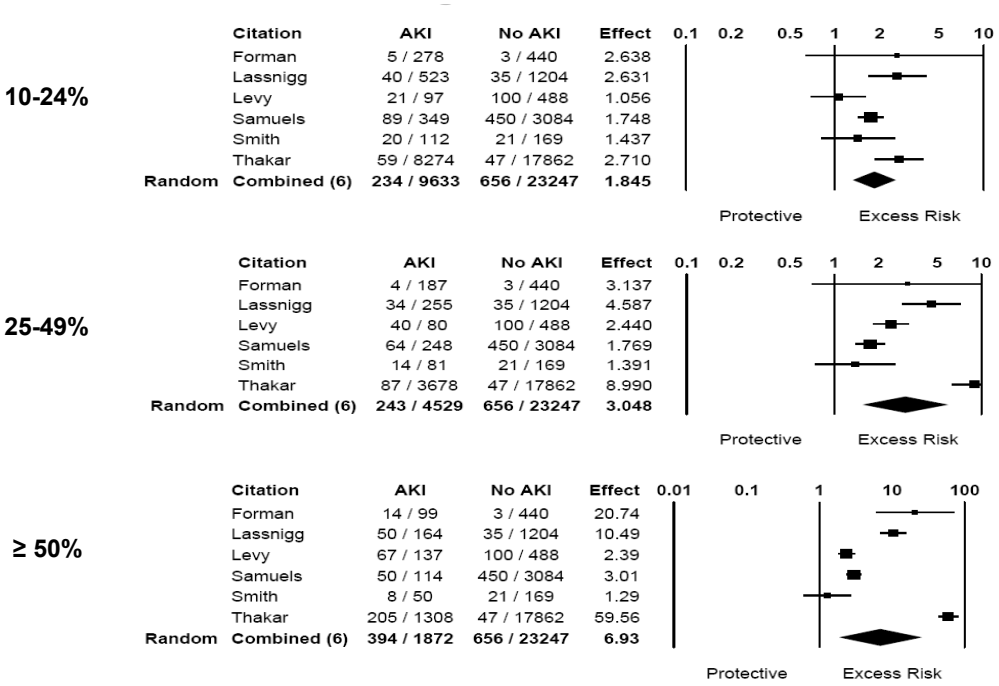


Figure 3. Short-term death associated with AKI (defined by *relative* increases in serum creatinine, mg/dL)

B.4. Long-term Natural History of AKI

B.4.1. Limited Long-term Data from Published Studies

The same investigators at Yale also conducted a systematic review and meta-analysis of the long-term outcomes after AKI. The review contained a total of 48 studies, of which 15 followed survivors of a hospitalization with and without AKI (based on various definitions of AKI).

Mortality. The mortality rate in these studies was 8.9 per 100 person-years for patients who survived hospitalization with AKI and 4.3 per 100 person-years for patients who survived hospitalization without AKI (Rate Ratio [RR] 2.62, 95% CI 1.99-3.45) **(**Figure 4**).**

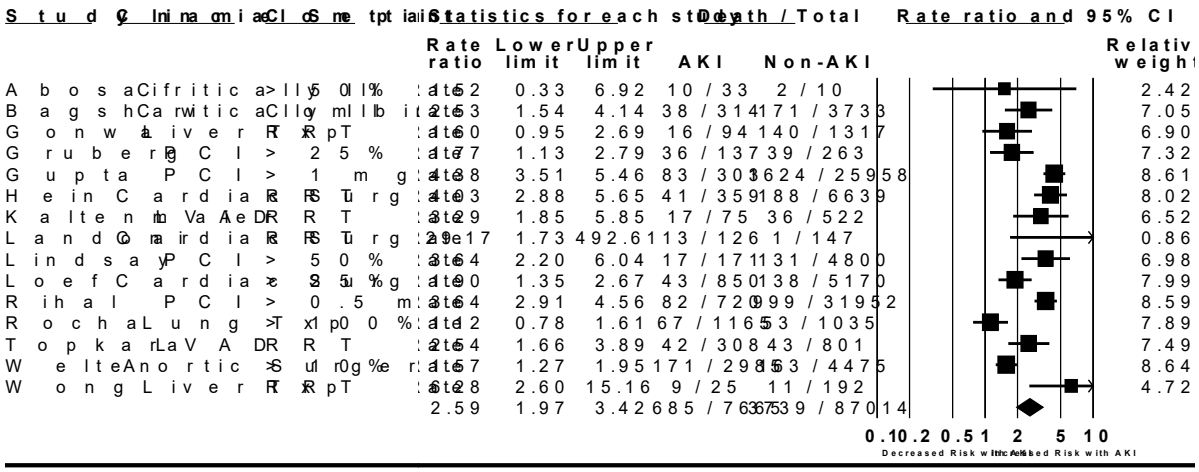


Figure 4. Pooled rate ratio for long-term mortality for survivors of a hospitalization with and without AKI.

Renal outcomes. Twenty nine studies provided data on the incidence of CKD or ESRD in patients who survived hospitalization with AKI. Twelve of these studies reported some form of CKD as an outcome, and 25 reported ESRD as an outcome (eight studies reported on both CKD and ESRD). The rate of CKD after an episode of AKI was 7.8 per 100 patient-years and the rate of ESRD was 4.9 per 100 patient-years. In studies that definitively excluded patients with pre-existing CKD, the rate of CKD after AKI was 6.2 per 100 person-years,[24,62-64] and the rate of ESRD was 4.2 per 100 person-years.[63,65-68] Two recently published studies have examined the risk of ESRD in patients with and without AKI. Newsome et al. demonstrated that the adjusted risk of ESRD associated with an increase in serum creatinine of 0.3 to 0.5 mg/dL was 2.36 and for an increase of 0.6 to 3.0 mg/dL the risk was 3.26 (95% CI 2.73-3.71).[69] Ishani et al. demonstrated that the adjusted hazard ratio for developing ESRD was 41.2 (95% CI 34.6-49.1) for Medicare patients who developed AKI in the setting of pre-existing CKD.[70] The relative risk of ESRD in patients with AKI without previous CKD (vs. no AKI) was 13.0 (95% CI 10.6-16.0), and for those with CKD without AKI was 8.4 (95% CI 7.4-9.6). Thus, AKI appears to accelerate progression of renal dysfunction, although several methodological limitations exist in published studies as described in more detail below.

B.4.2. Knowledge Gaps Regarding the Natural History of AKI

The majority of data for the studies described in *Section B.4.1* were collected retrospectively using existing health records and using varying methodology. The majority of the studies were single-center studies, thus limiting total achievable sample size and generalizability to the broader population of patients with AKI. Many studies did not report whether patients were lost to follow-up. Few studies followed patients without AKI and adequately adjusted for relevant confounding factors. Many different definitions were used for both AKI and CKD, complicating the comparison across studies and clinical application of the results published to date. Few studies excluded patients with prior CKD from the reported cumulative incidence of CKD. No studies examined the pattern or slope of GFR decline after AKI over time.

Many studies also did not have access to a previous true "baseline" measure of renal function—this critical weakness limits the ability of existing studies to determine accurately the occurrence of AKI and to evaluate the independent contribution of an AKI episode towards future adverse events. In addition, none of the studies examined the associations between acute-phase biomarkers of kidney injury and long-term outcomes. Studies that examine larger cohorts of patients with AKI with appropriately matched participants without AKI, repeated follow-up, and utilization of both continuous outcomes (measures of kidney function) and hard-outcomes such as CKD, ESRD, cardiovascular events, and death are needed to truly elucidate the consequences of AKI.

The ASSESS-AKI Consortium will directly address these important knowledge gaps.

B.5. Prognosis after AKI

B.5.1. Clinical Factors for Predicting Outcomes After AKI

While several investigators have utilized multivariable modeling to predict short-term risk of death after AKI,[21,68,71-74] few studies have examined the association with death among survivors of the index hospitalization. Limited data from six studies suggest that many non-renal factors may play a significant role in determining the long-term outcomes in patients who suffer an episode of AKI (Table 3).

Table 3. Predictors of Long-term Mortality after AKI.

Source	Lindsay, 2003*	Gruberg, 2000*	Gupta, 2005*	Loef, 2005	Welten, 2007	Schiffl, 2008
Clinical Setting	PCI	PCI	PCI	Cardiac Surgery	Aortic surgery	Critically Ill
Adjusted OR or HR for predictors of long-term mortality reported in manuscript						
AKI	2.7 (1.5-4.9)	3.9 (2.0-7.6)	1.8 (1.2-2.5)	1.6 (1.2-2.3)	1.7 (1.3-2.3)	N/A (no patients without AKI)
Acute Heart Failure	2.9 (1.2-6.9)	-	-	NS	NS	-
Age (per year)	2.1 (1.5-3.1)†	1.05 (1.05-1.09)	1.04 (1.03-1.05)‡	1.06 (1.04-1.09)	1.02 (1.01-1.03)	-
Prior myocardial infarction	2.1 (1.5-3.1)	-	-	NS	NS	-
Peripheral arterial disease	1.8 (1.2-2.6)	-	1.7 (1.4-2.0)	1.8 (1.2-2.6)	-	-
Chronic obstructive lung disease	-	-	1.8 (1.5-2.2)	-	1.8 (1.4-2.3)	-
Diabetes mellitus	NS	NS	1.5 (1.2-1.9)	NS	NS	-
Baseline CrCl (per 1 ml/min increase)	NS	NS	1.7 (1.3-2.2)*	0.99 (0.98-1.0)	0.99 (0.99-1.0)	-
Left ventricular ejection fraction	-	NS	0.97 (0.96-0.97)	-	-	-
Other factors listed	-	Vein graft location (1.6)	Hemoglobin (0.82); NYHA Class (1.1); Gender (1.2)	Duration of operation (1.004)	Stroke (1.5); RRT (2.6); Bleed (1.5); Statin (0.69)	Comorbidity (2.8) Surgery (1.6) CKD (4.1)

*OR reported, not HR †Age > 69 years ‡For every 10 years of age

B.5.2. Biomarkers for Predicting Outcomes After AKI

As noted in *Section B.2.2*, the majority of the focus in biomarker discovery and development has been on improving the diagnosis of AKI. Limited data exist on potential biomarkers that reliably predict clinical outcomes after an episode of AKI.

B.5.2.1. *Urinary NGAL and IL-18*

A study of 34 children with diarrhea-associated hemolytic uremic syndrome found that an elevated level of urinary NGAL (> 200 ng/ml) within the first five days of hospitalization possessed a sensitivity of 0.90, specificity of 0.54, positive predictive value (PPV) of 0.45, and negative predictive value (NPV) of 0.93 for the subsequent need for dialysis.[75] In another study of adult cardiac surgery patients,[39] the log of NGAL ng/ml at four hours and log of IL-18 pg/ml at four hours after cardiac surgery correlated with number of

days with AKI. In another cohort of children admitted to critical care units, urine NGAL and IL-18 performed moderately for predicting persistent AKI (duration > 48 hours). NGAL possessed a sensitivity of approximately 0.67 to 0.78 and specificity of approximately 0.67 to 0.69,[48] and IL-18 possessed a sensitivity of approximately 0.21 to 0.47 and a specificity of 0.71 to 0.93[40] for the diagnosis of persistent AKI. IL-18 has been demonstrated to be predictive of death in two studies. In the study of critically ill patients,[38] urinary IL-18 levels were significantly different on days 0, 1, and 3 between survivors and non-survivors (p= 0.04). A urine IL-18 value of > 200 pg/ml on day 0 in AKI participants was associated with an increased risk of death (HR 2.32, 95% CI 1.2-4.4) and was the strongest predictor of death after adjustment for APACHE II score and other baseline and clinical parameters. In children admitted to critical care units, urine IL-18 was independently associated with mortality (OR 1.29, 95% CI 1.01-1.64) after adjusting for severity of illness score.[40] In this same cohort, NGAL concentrations were not different between survivors and non-survivors.[48]

B.5.2.2. *Urinary KIM-1*

A recent study[76] examined the relationship between urinary KIM-1 and a composite endpoint of initiation of dialysis or death from any cause in a cohort of 201 hospitalized patients with AKI who had a nephrology consultation. Urinary KIM-1 level possessed an AUC of 0.61 for the prediction of the composite endpoint. The APACHE II score possessed an AUC of 0.78, which was increased marginally to 0.80 when KIM-1 level was added to the model. Higher quartile of KIM-1 level was associated with increased crude odds of the composite outcome, particularly for the highest compared with the lowest quartile: odds ratios for the 2nd, 3rd and 4th quartile (vs. 1st quartile): 1.4, 1.4, and 3.2, respectively. These associations were no longer significant after adjusting for potential confounders, so the independent prognostic value of KIM-1 for outcomes after AKI remains unclear.

B.5.2.3. *Urinary and Serum Cystatin C*

Cystatin C is metabolized by the proximal tubule and is undetectable in the urine under normal conditions. Elevated urinary cystatin C levels are predictive for the subsequent need for renal replacement therapy in patients with AKI (sensitivity 0.92, specificity 0.83, AUC 0.92).[58] The median time to initiation of renal replacement therapy was 4 days. Similarly, the magnitude of the change in serum cystatin C levels is predictive for the need for RRT (sensitivity 0.82, specificity 0.93, AUC 0.76), although study subjects had already met serum creatinine-based criteria for AKI when these changes in serum cystatin C occurred.[58] A single center study did not show an association between serum cystatin C levels and death, though this study focused on an ICU population, not just those with AKI.[77]

Overall, studies examining the association between biomarkers and long-term outcomes beyond hospitalization are currently lacking in the literature. The ASSESS-AKI Consortium will provide a unique longitudinal platform to delineate the relationships between biomarkers collected at different times and subsequent short- and long-term clinical outcomes.

B.6. Summary and Role of ASSESS-AKI

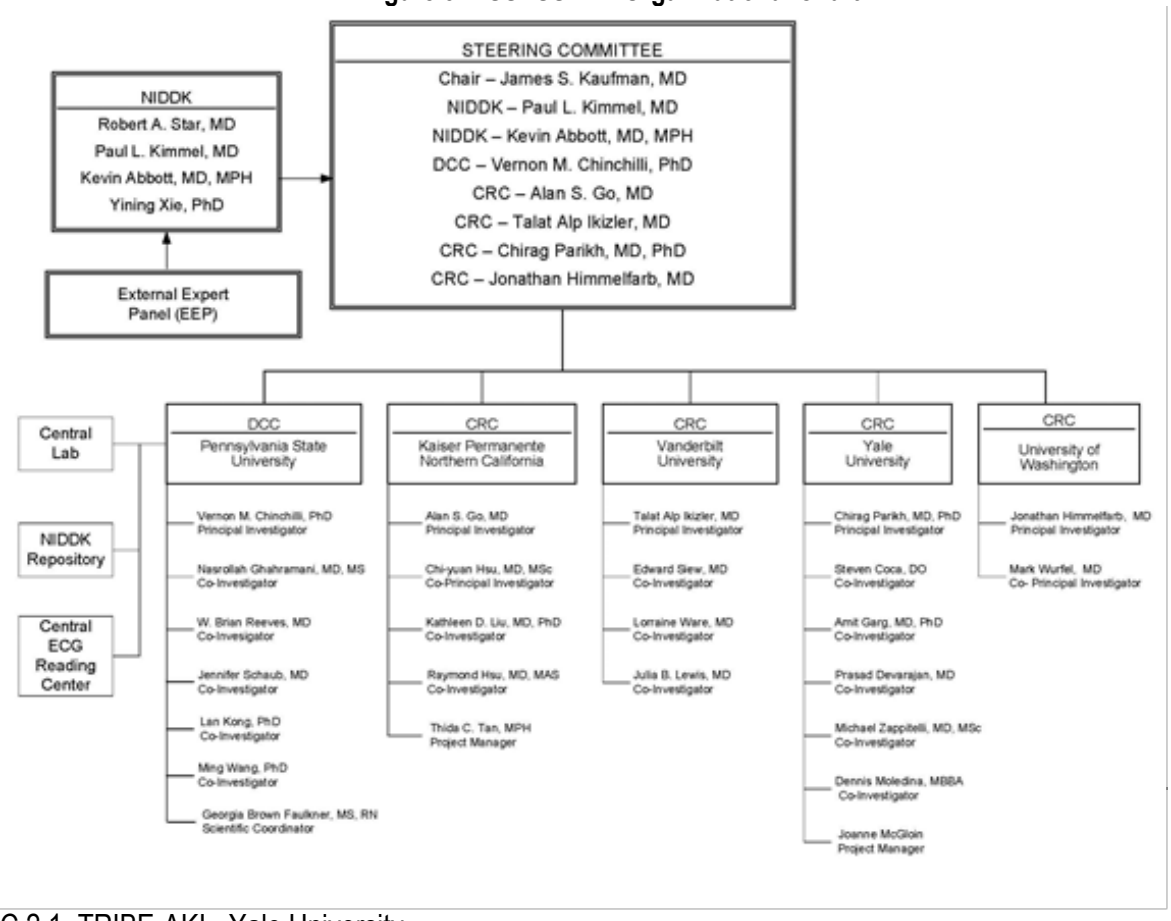
The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) have committed to address many of the existing knowledge gaps regarding AKI by establishing the Natural History of Acute Kidney Injury Consortium (RFA DK-07-009). The primary objective of this consortium is to follow the natural history of patients with acute kidney injury (AKI) after they finish the acute phase of their illness and compare with concurrent relevant patients who did not experience an AKI episode. The ASSESS-AKI Consortium was established in September 2008 and developed the present protocol to answer a series of critical research questions that are responsive to the RFA sponsored by NIDDK/NIH. Specific details about the organization and operations of the ASSESS-AKI Consortium are provided in *Section C* below.

C. ASSESS-AKI Consortium Organization

C.1. Consortium Organization

The organizational structure of the ASSESS-AKI Consortium is summarized in Figure 5. The ASSESS-AKI Consortium consists of a cooperative agreement between NIDDK/NIH, the four Clinical Research Centers (CRCs), and one Data Coordinating Center (DCC). The Consortium has a Steering Committee (SC), which is the main governing body to develop and direct its activities. An External Expert Panel (EEP) provides input to NIDDK regarding the progress of the consortium. The ASSESS-AKI Consortium includes ancillary efforts to NIH-funded studies in progress at the four CRCs: TRIBE, an ongoing multi-center study examines timed renal injury after cardiac surgery; VALID, an ongoing ICU-based clinical study of more complex 'un-timed' forms of AKI in the setting of severe illness; Kaiser Permanente of Northern California, an ongoing longitudinal study of the epidemiology and outcomes of AKI within a large community-based population involving patients hospitalized in different settings; and the University of Washington, which will be initiating a prospective cohort study to identify genetic variants that predict higher susceptibility to AKI, recovery of kidney function after the development of AKI, and higher rates of progression from AKI to CKD.

Figure 5. ASSESS-AKI Organizational Chart



C.2.1. TRIBE-AKI - Yale University

The study will be conducted under the leadership of Dr. Chirag Parikh at Yale University who is also the PI of the TRIBE-AKI Study (see *Section D.2.1* for study details). Co-investigators include Drs. Steven Coca, Amit Garg, Prasad Devarajan, and Michael Zappitelli, and Dennis Moledina, MBBA. The research coordinator is Joanne McGloin. All team members will be involved in each stage of the research process, and critical interactions will be facilitated by bi-weekly scheduled meetings of all key personnel as members of the site steering committee. Meetings between the Yale investigators and the other PIs at the sites in the existing TRIBE-AKI consortium occur on a monthly basis. In addition, a call between all site coordinators occurs on a weekly basis.

C.2.2. VALID - Vanderbilt University Medical Center

The study will be conducted under the leadership of Drs. Alp Ikizler and Edward Siew. The project was initially started as an ancillary study to the VALID Study (see *Section D.2.2* for study details) and subsequently expanded to all patients admitted to VUMC. Other co-investigators are Drs. Lorraine Ware and Julia B. Lewis. All team members will be involved in each stage of the research process, and critical interactions will be facilitated by bi-weekly scheduled meetings of all key personnel as members of the site steering committee. During these meetings, personnel will update all investigators on key aspects of patient visits, retention, assay quality control, and analysis. Administrative details including scheduling, and ordering of laboratory and office supplies will be done by Dr. Charles Ellis and administrative staff. Dr. Ellis will coordinate all data and specimen transfer to the DCC and the NIDDK Biorepository under the supervision of Dr. Ikizler.

C.2.3. Kaiser Permanente of Northern California

The Kaiser Permanente of Northern California (Kaiser) CRC will be an extension of an ongoing collaboration between the Kaiser Departments of Research, Divisions of Nephrology within The Permanente Medical Group, and the Division of Nephrology at UCSF (see *Section D.2.3* for details). The Kaiser CRC will be led by Dr. Alan S. Go who will take responsibility for all administrative, protocol, and clinical responsibilities. Dr. Go will be supported by Dr. Chi-yuan Hsu at UCSF (Co-PI), and Dr. Kathleen Liu at UCSF (Co-I), who provide complementary content, methodological, and operational expertise, and Dr. Raymond Hsu at UCSF (Co-I). The organization of the Kaiser CRC is summarized in Figure 6 below:

KPNC-UCSF Clinical Research Center Organization

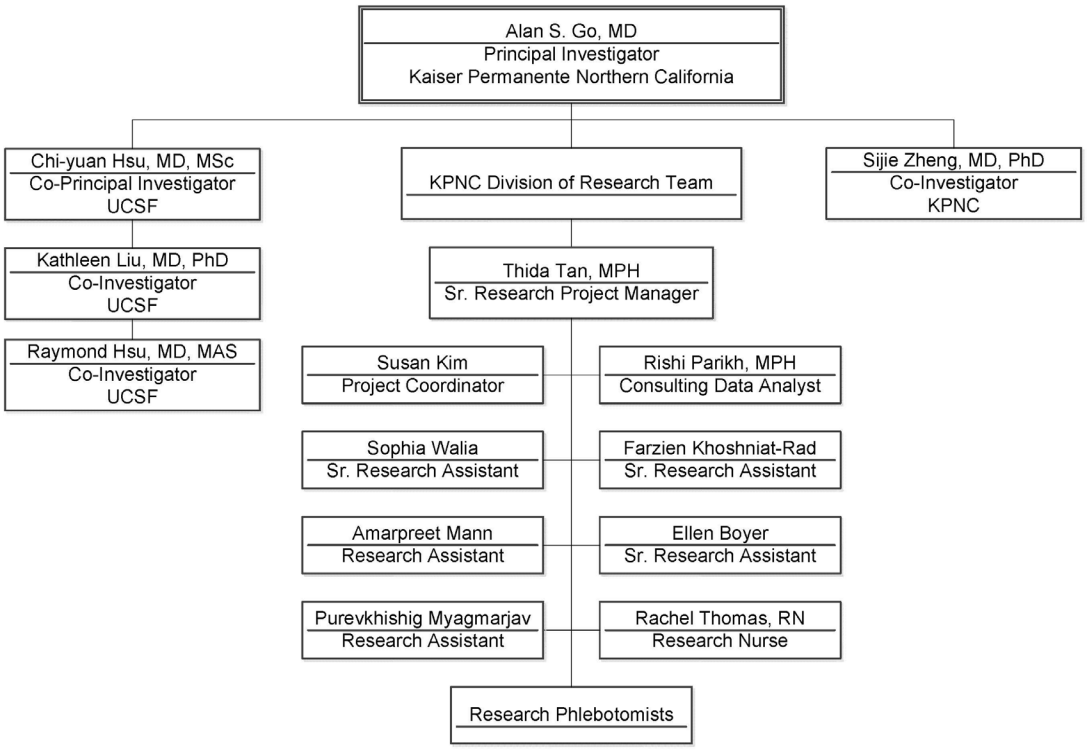


Figure 6. Organizational Structure of the Kaiser Permanente of Northern California CRC

The Kaiser CRC will be highly integrated with weekly meetings among the Kaiser study team and monthly meetings among the entire CRC team. In addition, Dr. Go will be in frequent e-mail and phone contact with Drs. Hsu, and Liu to address any scientific, clinical, or critical operational issues.

All study protocol elements (administrative and clinical) are implemented through the Kaiser team with overall supervision by Dr. Go. For all study components, the Project Manager will be supported by the study Project Coordinator, Research Assistants, Data Consultant, and Research phlebotomists.

C.2.4. University of Washington

This Ancillary Study will be under the direction of Jonathan Himmelfarb MD (PI, Nephrology) and Mark Wurfel, MD, PhD (Co-PI) Pulmonary & Critical Care). They will capitalize upon their combined expertise in AKI, CKD, critical care medicine, genetic analyses, and bioinformatics. The study will take advantage of collaborations with two consortiums; an ongoing independent multi-center genome wide association studies consortium in critically ill patients (iSPAAR Consortium), and with a general population consortium (CDGgen Consortium). The consortiums will enable validation and replication of study findings. The study team will also include a Study Coordinator and a Research RN, who will together focus on enrollment, data collection and entry, patient tracking and scheduling, and all other aspects of actualizing a successful study.

C.3. Data Coordinating Center (DCC)

The Department of Public Health Sciences (DPHS) and the Division of Nephrology in the Department of Medicine at The Pennsylvania State University College of Medicine, Hershey, serves as the DCC for ASSESS-AKI. Vernon Chinchilli, PhD oversees the DCC as the PI. The Co-Investigators include nephrologists, Nasrollah Ghahramani, MD, MS, W. Brian Reeves, MD, and Jennifer Schaub, MD and biostatisticians, Lan Kong, PhD and Ming Wang, PhD.

The DCC provides leadership for the biostatistical aspects of optimizing study designs for increased accuracy and precision, projecting sample sizes, selecting and implementing sampling schemes, assisting in defining the primary and secondary outcomes and analytical approaches for the protocols, executing the statistical analyses of study data, serving as a central repository for data generated from the Clinical Research Centers (CRCs), developing the presentations/publications, and preparing the confidential data analyses and reports for the External Expert Panel (EEP). The DCC establishes and manages the computer network, a secure and confidential computerized system to collect study data, including cardiac imaging data. The network operates via the Internet and World Wide Web and integrates quality assurance measures and the capability to produce data reports.

The DCC team provides scientific coordination for the CRCs, which includes collaborating with the ASSESS-AKI investigators on protocol development and implementation; overseeing the informed consent process; preparing, and leading the training sessions; overseeing quality control site visits; and establishing the certification criteria for ASSESS-AKI procedures. The DCC assumes primary responsibility for preparing the reports, presentations, and publications. The DCC identifies, secures, and provides appropriate oversight to the subcontracts for Central Laboratories and other adjuncts to the study on behalf of ASSESS-AKI; administers systems for sample collection, distribution, and storage of biological specimens and cardiac images. The DCC provides project management and administrative support that includes developing an effective organizational structure; facilitating orientation of all members; tracking project timelines and resources; coordinating the conferences, meetings, and presentations; and providing editorial and clerical assistance with publications. The DCC also leads the Consortium in addressing analytic issues.

The DCC coordinates activities of the committees, which includes at a minimum, Steering, Quality Control, Coordinator, Biomarker Partners, Event Adjudication, Ancillary Studies, and Presentations and Publications. The DCC assumes administrative responsibility for responding to the funding and regulatory agencies. The DCC provides recruitment support and tracking to the CRCs, working with the CRC to tailor the most effective recruitment strategy. Based on the eligibility criteria determined by the Steering Committee, the recruitment strategies are regularly monitored, modified, and updated for consistency.

C.4. Core Measurement Laboratory and Reading Centers

The DCC serves as the Consortium liaison to external entities, such as a central laboratory, equipment vendors, and pharmaceutical, medical device, and biotechnology companies. The DCC will establish, via subcontracts, central and partner laboratories and reading centers, as deemed necessary by the study protocol. It will provide administrative coordination for the storage, retrieval, processing, and testing of biological specimens obtained from cohort study participants.

D. STUDY DESIGN AND METHODS

D.1. Study Design

ASSESS-AKI will employ a parallel matched prospective cohort of participants with AKI and matched adult participants without AKI to address the proposed Specific Aims. In addition, ASSESS-AKI will use a prospective cohort design and attempt to enroll all eligible children undergoing cardiac surgery as part of the TRIBE-AKI Study. Throughout the remainder of the protocol, we note specifically when there are differences between adult and pediatric ASSESS-AKI participants.

The selected study designs were chosen primarily to answer the primary Specific Aims 1 and 2 in the most efficient manner within the constraints of available resources. ASSESS-AKI will take advantage of existing research efforts involving AKI within participating Clinical Research Centers (CRCs) to identify, recruit, and follow hospitalized participants who do or do not appear to have suffered an episode of AKI based on serum creatinine-based definitions. In its deliberations, the Steering Committee discussed the following principles in considering the final study design and participant selection.

With regard to participants who suffered an inpatient episode of AKI, the Steering Committee identified that the enrolled population should include:

- A wide spectrum of severity of AKI, as currently defined by the magnitude of change in peak inpatient serum creatinine compared with baseline outpatient serum creatinine concentration.
- An acceptable spectrum of type of AKI, broadly characterized as acute tubular necrosis, pre-renal azotemia, and other/unknown.
- A final population distribution that could be achieved across CRCs within a relatively short recruitment period to maximize long-term follow-up.

With regard to participants who did not experience an inpatient episode of AKI, the Steering Committee identified that the enrolled population should:

- Have minimal or no relative and absolute change in peak inpatient serum creatinine compared with baseline outpatient serum creatinine concentration to enhance the likely separation in subsequent event rates during follow-up.
- Be very similar to those with AKI with regard to major baseline confounders based on a prioritized set of criteria used to match individual participants.
- Have a high likelihood of completing long-term follow-up.

D.2. Overview of source populations

In the following sections, we provide details about the parent studies and source populations at each of the participating CRCs.

D.2.1. TRIBE-AKI

The **Translational Research Investigating Biomarker Endpoints in AKI Network (TRIBE-AKI) Study** is in the process of validating novel biomarkers for AKI following cardiac surgery. Dr. Chirag Parikh is the PI and Yale is the data- and sample-coordinating center. The study is sponsored by NHLBI (HL085757) and was initiated in May 2007. There are a total of seven sites in the TRIBE-AKI study (Figure 7). The sites include: Yale University, Duke University, University of Colorado Health Sciences Center, University of Chicago, London Health Sciences Center (Ontario), University of Cincinnati Children's Hospital (pediatric site), and Montreal Children's Hospital (pediatric site) Two adult sites (Yale and Ontario) and both pediatric sites will participate in ASSESS-AKI.

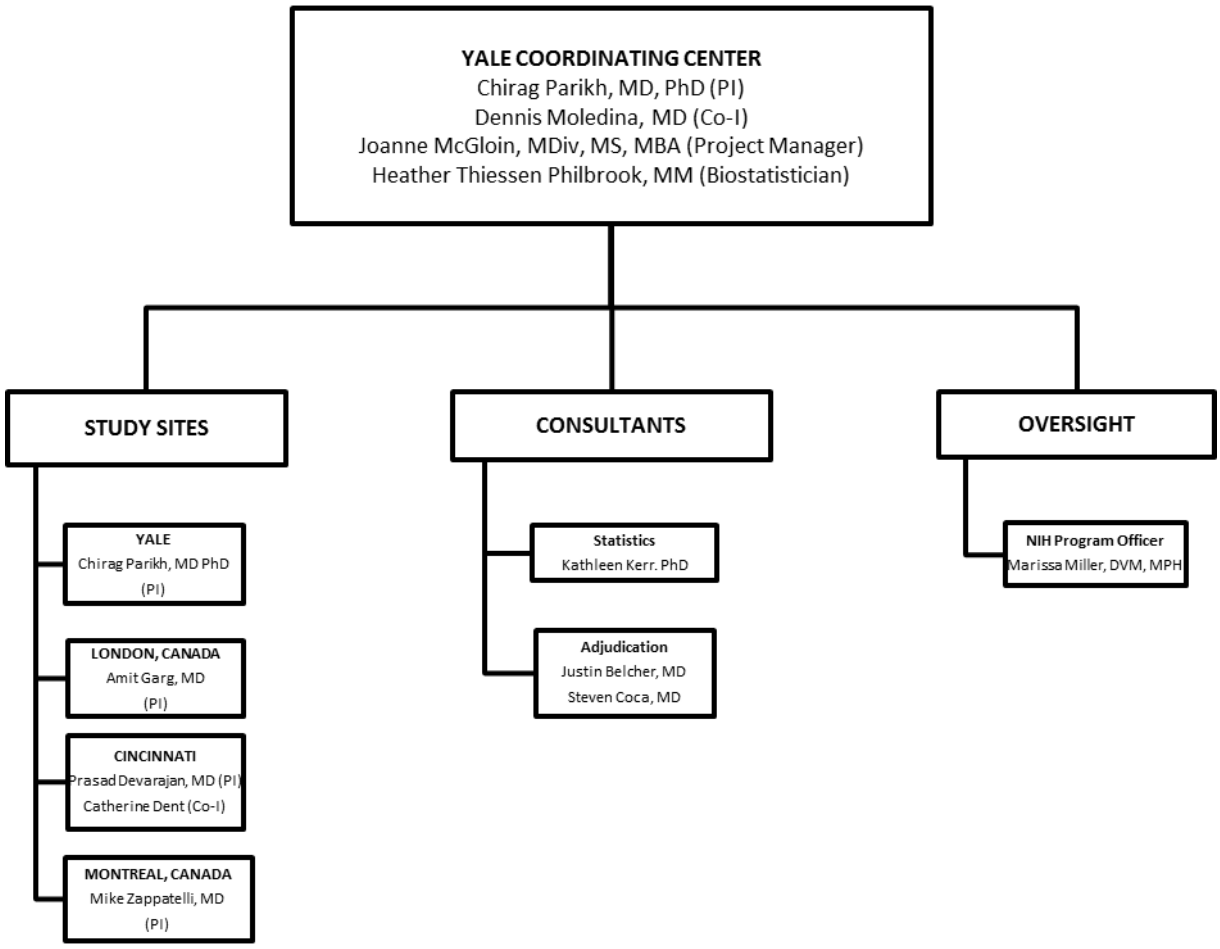


Figure 7. TRIBE-AKI Organizational Chart

Since the TRIBE-AKI study has already fulfilled all of its targets for enrollment by the time ASSESS-AKI commenced official enrollment, enrollment of new participants for the ASSESS-AKI study will occur by

two methods (method A and method B). Method A will involve approaching the potential participant prior to their cardiac surgery. These potential participants are screened through cardiac surgery clinics of the collaborating cardiac surgeons in the greater New Haven area. Patients meeting the following inclusion and exclusion criteria will be approached:

Inclusion Criteria:

- All patients admitted for elective, urgent, or emergent coronary artery bypass (CABG) surgery and/or cardiac valve surgery

Exclusion Criteria:

- Any cardiac surgery where preoperative AKI cannot be reliably excluded
- Cardiac transplantation, or insertion of left ventricular assist device
- Pre-operative serum creatinine level >4.5 mg/dL (400 μmol/L) or on chronic dialysis
- Administration of intravenous contrast within 48 hours preceding cardiac surgery
- Evidence of AKI prior to surgery (defined as >0.5 mg/dL increase in serum creatinine concentration from preadmission to initiation of the cardiac surgery)
- Enrolled in another research study which may affect measurements or outcomes of this study
- Prior renal transplantation
- Acute infective endocarditis
- Nephrotoxic drugs administered pre-operatively (e.g., aminoglycosides, amphotericin)

Participants enrolled via method A in the TRIBE-AKI study will have both pre-operative and post-operative blood and urine samples collected, as summarized in Figure 8:

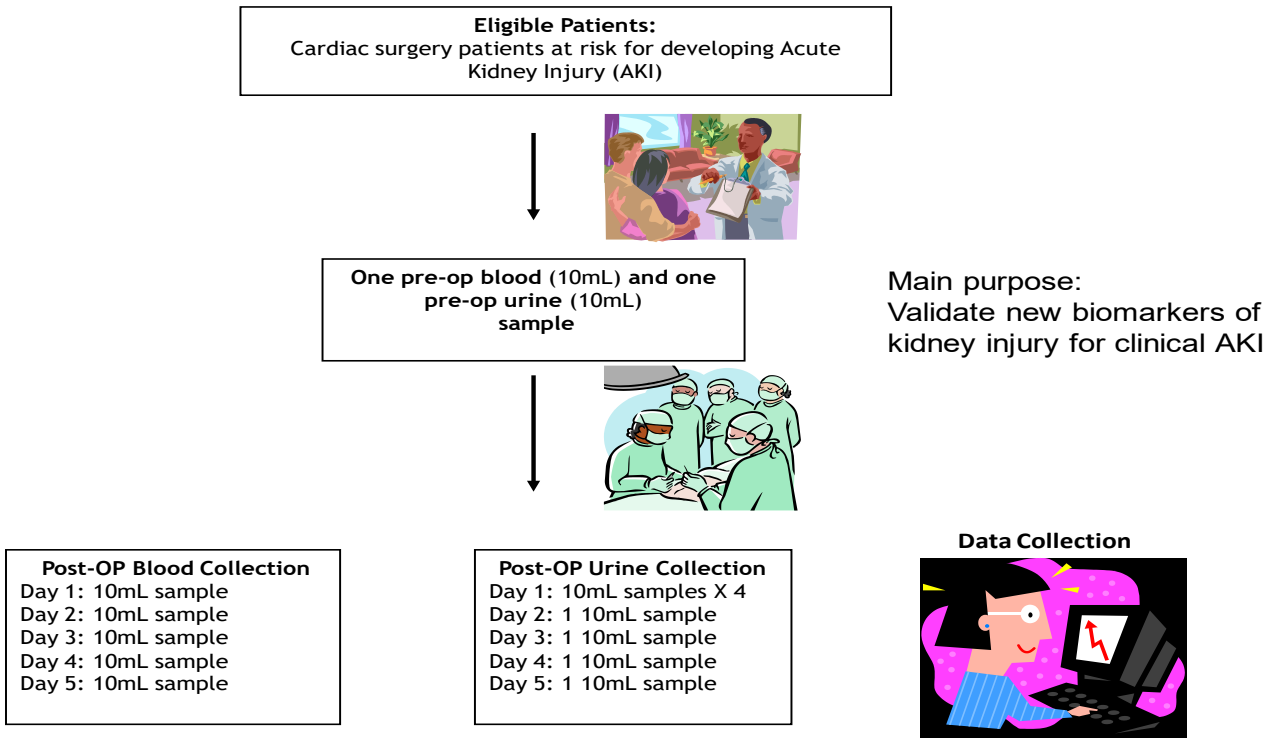


Figure 8. Summary of TRIBE-AKI enrollment and specimen collection protocol.

The post-operative samples are collected daily for five days. These specimens are spun, aliquoted, labeled, and frozen at -80°C. The main exposure in the TRIBE-AKI study is the concentration of serum and urine biomarkers and AKI is the primary outcome. Since AKI is the primary outcome, very careful attention is given to variables such as baseline and serial serum creatinine level ascertainment. Serial urine output is also collected in all participants, which helps distinguish between oliguric and non-oliguric AKI. Moreover, all the variables that may help define the etiology of AKI are collected such as diuretic doses during hospitalization, cardio-pulmonary bypass time, and contrast administration.

Method B of enrollment will only be utilized at Yale-New Haven Hospital. Method B will involve approaching all adult subjects in the cardiothoracic intensive care unit that meet the following criteria:

1. Has had cardiac surgery on this admission for CABG, valve or aneurysm
2. Has had an increase in serum creatinine of at least 0.3mg/dL or at least 50% from baseline

Exclusion criteria are identical to method A of enrollment. Informed consent will be obtained in the CT-ICU at such time that the patient has experienced a rise in creatinine level and is able to consent to participation.

All other protocol steps will be identical to participants enrolled through method A with the exception of blood/urine sampling prior to and immediately following surgery, since enrollment will be delayed. For method B, the specimen collection will begin on the day of consent (the same day that a rise in serum creatinine was detected); all succeeding sample collections will be identical to those participants enrolled from method A.

This separate group of subjects is added in order to enrich the number of subjects with AKI that can participate in ASSESS-AKI.

Table 4 summarizes selected characteristics of the first 791 adult patients who were enrolled into the parent TRIBE-AKI Study.

Table 4. Baseline characteristics and in-hospital outcomes among the first 791 adult patients enrolled in the TRIBE-AKI Study

	All (N=791)	AKI (N=237)	No AKI (N=553)
Demographics			
Age (adults), years	70.3 ± 10.5	69.6 ± 11.2	70.6 ± 10.2
Women	30%	28%	30%
White Race	90%	89%	90%
Type of Surgery			
CABG	59%	54%	61%
CABG & Valve	14%	14%	14%
Cardiac transplant	1%	2%	1%
Other	6%	7%	5%
Valve	21%	24%	20%
Timing of Surgery			
Elective	74%	62%	79%
Emergent	6%	6%	6%
Urgent	20%	32%	15%
Kidney Variables			
Baseline SCr, mg/dl	1.1 ± 0.3	1.3 ± 0.4	1.1 ± 0.3
Baseline eGFR	69 ± 21	63 ± 23	70 ± 19
Peak SCr, mg/dl	1.4 ± 0.7	2 ± 1	1.2 ± 0.3
Discharge SCr, mg/dl	1.1 ± 0.4	1.5 ± 0.7	1 ± 0.2
Outcomes			
ICU stay, days	2.9 ± 2.5	4.2 ± 4.2	2.4 ± 1.3
Hospital stay, days	7.9 ± 7.1	11 ± 10.5	6.7 ± 5
Deaths	3%	9%	1%

As demonstrated above, TRIBE-AKI has enrolled to date an older, predominately white cohort. Nearly three quarters of the cardiac surgeries are elective and pre-operative mean eGFR is ~70 ml/min/1.73m^2.

For ASSESS-AKI, participants will only be recruited from four of the seven sites in TRIBE-AKI (Yale University, London Health Sciences Center [Ontario], University of Cincinnati Children's Hospital, and Montreal Children's Hospital).

D.2.2. VALID

The **Validation of Acute Lung Injury Biomarkers for Diagnosis (VALID) Study** is an ongoing NHLBI funded (HL081332) prospective observational study that has been undertaken by the Vanderbilt Clinical Proteomics Program. Dr. Lorraine Ware, a Co-Investigator in ASSESS-AKI, is the PI of VALID. The study is designed to collect blood and urine samples from 2550 well-phenotyped critically ill patients with the

goal of developing and validating a panel of plasma biomarkers for the clinical diagnosis of acute lung injury and the acute respiratory distress syndrome. The VALID study is a novel and unique resource that is ideally suited for the proposed studies of acute and chronic kidney disease. The VALID cohort includes a diverse population of critically ill patients that are at high risk for developing AKI among hospitalized patients. Although all patients in the cohort are at risk for AKI by virtue of their critical illness, only a fraction develops AKI. Thus, a diverse and well matched population of participants without AKI will be identified prospectively and will be followed longitudinally in parallel with the AKI cohort. Furthermore, the participants in this cohort are included largely on the basis of critical illness. The absence of major exclusion criteria render this a highly generalizable study population, in contrast to cohorts drawn from clinical trials. In addition, longitudinal follow-up is anticipated to be feasible in the majority of participants with or without AKI, as evidenced by the high degree of success of other longitudinal follow-up studies conducted in patients drawn from the same ICU population at Vanderbilt University Medical Center.

Participants are enrolled into the VALID study in the medical, surgical, and trauma ICUs at Vanderbilt on ICU day 2 provided they are not expected to leave the ICU that same day. Patients are assessed daily for development of relevant clinical diagnoses, including acute lung injury, acute respiratory distress syndrome, sepsis, and AKI. A rich database of important clinical covariates is collected prospectively, including hemodynamic data, ventilator settings, fluid balance, laboratory values, medications, and medical history. Important clinical outcomes, including organ failures, death, duration of ICU stay, duration of hospital stay, and need for dialysis, are recorded. In the parent study protocol, blood is currently collected at study enrollment on ICU day 2 and subsequent sampling on ICU day 4 with urine samples collected daily on days 1 through 5 and weekly thereafter. Strict standard operating procedures have been instituted to ensure that the biological samples are of high quality for both discovery and targeted biomarker studies. For ASSESS AKI, participants are also enrolled outside of the ICU.

D.2.3. Kaiser Permanente of Northern California

The **Kaiser Permanente of Northern California (Kaiser) Division of Research** in collaboration with the University of California, San Francisco (UCSF) has been conducting a series of NIDDK-sponsored (DK067126) longitudinal studies characterizing the epidemiology and outcomes of acute, chronic, and end-stage renal disease within Kaiser's large and diverse community-based population. Kaiser has been in existence since 1945 and is one of the largest integrated health care delivery systems in the U.S. As of December 2008, Kaiser provides care for 3.3 million members that are ethnically and socioeconomically diverse and highly representative of the northern California and statewide population. Kaiser delivers comprehensive inpatient and outpatient care to its members and captures many aspects of its care through the use of its comprehensive clinical and administrative databases, which will be leveraged for ASSESS-AKI. Kaiser's regional Division of Research will lead and coordinate all study activities through Dr. Alan Go. In-hospital study activities will occur at up to four Kaiser hospitals with follow-up activities at the Division of Research clinical exam and laboratory facilities.

The relevant electronic and other data sources that will be used for identification of eligible participants for ASSESS-AKI are described briefly below. It is important to emphasize that the Kaiser electronic data sources we propose to use are more comprehensive than usual administrative/claims databases and we have successfully used them for effective recruitment of specific types of patients and to enhance event ascertainment, long-term follow-up and surveillance for study participants.

- *Subject tracking across Kaiser databases*. A unique medical record number remains with each member throughout his or her lifetime, regardless of length or continuity of membership, and is used to link across all available health plan databases and electronic medical record.

- *Demographic characteristics*. This database includes complete information on date of birth, self-reported gender, primary residential address, and telephone contact information.

- *Laboratory tests*. All laboratory tests are financially covered as part of the basic Kaiser membership benefits. A region-wide lab database has been in place since 1994, with daily updates of laboratory results. Essentially all inpatient and outpatient laboratory test results are performed at, or captured through, the regional laboratory that conducts routine quality assurance checks in compliance with state and national standards. All laboratory tests performed at individual Kaiser hospitals utilize the same protocols and reagents as the regional laboratory. As of January 28, 2008, Kaiser moved to routine use of the IDMS calibrated serum creatinine assay which will facilitate direct comparisons with the ASSESS-AKI Central Laboratory.

- *Renal replacement therapy*. Persons who require maintenance peritoneal dialysis or hemodialysis or who undergo kidney transplantation are systematically tracked through a health plan registry that identifies when patients start (and stop) chronic dialysis, type of dialysis, and the date(s) of renal transplantation.[78] Since Kaiser is financially responsible for these services, the registry captures all members who require these therapies. Information on chronic renal replacement therapy dates back to the 1970's. This registry has been evaluated against the USRDS[8,79] and will be used to identify patients with prior renal replacement therapy and assist with prospective surveillance of enrolled participants in ASSESS-AKI.

- *Ambulatory care/diagnostic information and electronic medical record*. An automated database of all ambulatory encounters (e.g., outpatient clinics, urgent care, and emergency department visits) has been available since 1995. In addition, Kaiser is completing implementation of a region wide electronic medical record. The electronic medical record will capture all elements of medical care, including inpatient and outpatient progress notes as well as imaging and procedure data to facilitate rapid access to relevant records for event adjudication in our study cohort as well as characterizing prior morbidity.

- *Hospital-based care and diagnostic information*. Comprehensive databases of ICD-9-CM-based discharge diagnoses and procedures for admissions to Kaiser hospitals are routinely available since 1981. Similarly, billing claim data for emergent care provided at non-Kaiser hospitals have been available for >15 years and contain relevant discharge diagnosis and procedure codes. Of note, <10% of hospitalizations among members occur at a non-Kaiser facility, and the majority are repatriated to a Kaiser hospital early in their clinical course to complete their hospitalization, which allows capture of relevant diagnoses and the majority of procedures performed in this small subgroup of patients.

D.2.4. University of Washington

The "Genetic Determinants of Outcomes in Acute Kidney Injury" study at the **University of Washington** is an ancillary investigation focused on the need for new molecular and genetic markers of risk for poor outcomes in AKI with the goal of identifying patients who might benefit from more aggressive care or new therapies. The first aim of this study will be to contribute new patients to the ASSESS AKI consortium, enrolling patients with sepsis or who have suffered traumatic injury who are admitted to the intensive care unit (ICU) at Harborview Medical Center (HMC) and who are at high risk for development of AKI and following AKI participants and matched non-AKI participants through the previously-defined follow up period. The University of Washington study builds on existing resources and mechanisms developed as part of the Harborview Medical Center Trauma and SIRS ICU Genomics studies directed by Drs. Mark Wurfel and Grant O'Keefe (both Co-investigators on this project) as part projects previously funded by the NHLBI and NIGMS. Enrollment and data collection will be facilitated by automated queries of the comprehensive electronic medical record (EMR) at HMC developed as part of Dr. Wurfel's previous studies. Patients will be screened for enrollment after admission to the ICU. Patients not meeting exclusion criteria will be consented for ongoing in-hospital follow-up and search of their pre-hospital medical record for qualifying creatinine measurements. An automated EMR monitoring system will alert study staff of the development of AKI in enrolled individuals at which time mandated samples will be collected. These subjects who develop AKI will then be consented for post-hospital follow-up. Appropriately matched non-AKI participants who do not develop AKI will be selected from the remaining cohort. Follow-up will occur in the Nephrology Outpatient clinic at HMC in dedicated research space. Longitudinal follow-up is anticipated to be feasible in the majority of participants with or without AKI, as evidenced by the high degree of success of other longitudinal follow-up studies conducted in patients drawn from the same ICU population at HMC.

As part of studies in Aims 1 and 2, the University of Washington site will direct a genome-wide association study (GWAS) in all adult ASSESS-AKI Consortium subjects comparing AKI participants and non-AKI participants to identify genetic loci influencing risks for developing AKI (Aim 1) as well as risk for developing progressive CKD once an episode of AKI has occurred (Aim 2). The loci that alter susceptibility to AKI of will then be validated using an independent multi-center cohort (iSPAAR Consortium, Wurfel Co-PI) of critically ill patients. Loci influencing the risk for developing progressive CKD after an episode of AKI will be identified as well and validated with existing de-identified data from the CKDGen Consortium. Serum and urine quantitative biomarkers will be analyzed as potential intermediate phenotypes explaining genotype-AKI relationships as well as genotype-CKD relationships.

D.3. ASSESS-AKI Inclusion and Exclusion Criteria.

In the following sections, we describe the inclusion and exclusion criteria for the study cohort along with the rationale for key design decisions. Overall, the CRC PI will be responsible for confirming and documenting final participant eligibility before enrollment into ASSESS-AKI.

D.3.1. Inclusion Criteria

- Adults aged 18 years to 89 years will be considered eligible. An upper age limit was selected in order to reduce the effects of competing risks on the ability to examine the impact of AKI on various clinical

outcomes and to enhance the likelihood of complete follow-up.

- Children will also be enrolled only through the TRIBE-AKI Study, and they will be defined as age greater than one month to less than 18 years old at cohort entry.

- Hospitalized at one of the participating ASSESS-AKI CRC sites.

- Only patients with known information on "baseline" serum creatinine and estimated GFR using the CKD-EPI estimating equation[80] will be included. Operationally, the "baseline" serum creatinine concentration for each subject will be considered the outpatient, non-emergency department test value nearest to the index hospitalization within 365 days prior to admission using an IDMS calibrated serum creatinine assay.

    - If an outside laboratory is using the Siemens/Dade Dimension or NOVA whole blood analyzer, the serum creatinine value may not be used and is not considered to be IDMS calibrated.
    - If a person has more than one available test result, the information will be collected but the results will not be averaged.
    - It is recognized that there is error in the MDRD GFR estimating equation[81] as well as more recent estimating equations such as CKD-EPI[80] and that the study will be relying on test results obtained as part of clinical care rather than through a screening protocol. However, the rationale for this approach is based on preliminary data from the three CRCs demonstrating that the vast majority of potentially eligible participants do not have more than two to three pre-admission serum creatinine values during this time frame and that the most recent value is more likely to reflect the subject's "baseline" kidney function before the index hospitalization.
    - The TRIBE-AKI Study, pre-operative serum creatinine results from an IDMS calibrated assay obtained within seven days before cardiac surgery can be used to define "baseline" kidney function for the subset of participants who are undergoing non-urgent cardiac surgery.
    - In addition, for pediatric participants in TRIBE-AKI, we will accept a pre-operative serum creatinine concentration measured in the local hospital clinical laboratory among patients scheduled for elective cardiac surgery. We note that the two participating pediatric recruitment sites (Cincinnati and Montreal) currently use the Jaffe method for measuring serum creatinine.

ASSESS-AKI presents an unprecedented opportunity to improve the research methodology for studying the epidemiology of AKI, and these methodological considerations have directly influenced the final study design of the planned prospective cohort. One such consideration that has not received adequate attention in existing AKI literature is the issue of defining "baseline" kidney function among patients who suffer an episode of AKI. It is well known clinically that patients with pre-existing CKD are at high risk for AKI. However, a careful review of the methods used by existing clinical AKI studies makes it clear there was no uniform definition for what was considered "baseline" kidney function before an episode of AKI. Some studies use the lowest serum creatinine observed during the hospitalization,[82,83] while others rely on the lowest of the first three inpatient serum creatinine readings,[11] the serum creatinine concentration measured immediately before a surgical procedure,[84,85] or whatever pre-admission or nadir serum creatinine data

were available.[86] The lack of rigor in defining "baseline" kidney function is problematic for numerous reasons. For example, if the "baseline" serum creatinine actually reflects incipient AKI, this will exaggerate the association between "baseline" kidney function and risk of AKI.

In studying the natural history of AKI, it is especially important to establish as reliably as possible the level of kidney function before AKI. This is particularly critical in studies designed to examine the impact of AKI on the subsequent trajectory of kidney function among persons with AKI compared with those without AKI, such as ASSESS-AKI. Since baseline kidney disease is a strong risk factor for AKI, differences in true baseline kidney function must be well delineated. Otherwise, it can be nearly impossible to tell how much of any observed difference in the subsequent trajectory of kidney function between participants with and without AKI is because of AKI rather than confounding by differences in their baseline trajectory of kidney function. For example, if it is observed that patients who suffer AKI are more likely to develop ESRD in the three years after discharge compared with hospitalized patients who did not suffer AKI, this may simply be because patients who suffered AKI had a lower pre-hospital GFR and steeper pre-admission GFR slopes than non-AKI participants, and AKI was merely a marker for the severity of underlying kidney disease. This is illustrated in Figure 9.

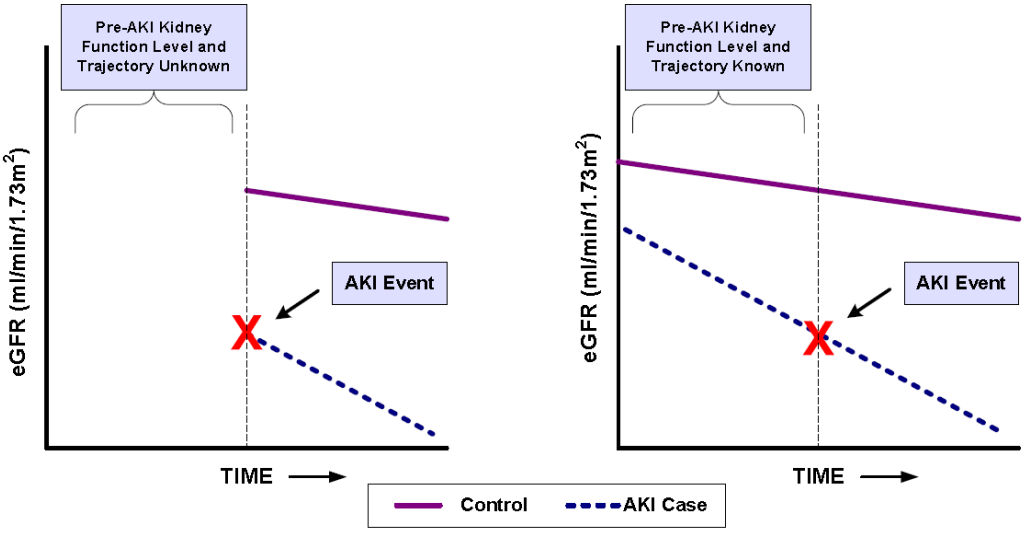


Figure 9. Importance of knowing the level of kidney function and trajectory of kidney function decline before an episode of AKI to be able to interpret the independent effect of AKI on subsequent kidney function. The panels represent the problem of examining the clinical course after AKI without prior information on kidney function.

In addition, empirical data from Kaiser Permanente of Northern California demonstrate that among ~29,000 adult members hospitalized between January 2006 and June 2007 and who had at least two prior available outpatient serum creatinine measures during the 24 months prior to admission, approximately 24% were observed to have a *decrease* in their first inpatient serum creatinine concentration. These data demonstrate one of the significant pitfalls in prior studies of AKI that have relied on the first admission serum creatinine as the "baseline" level of kidney function.

D.3.2. Exclusion Criteria

Below are the specific exclusion criteria which were selected to balance the goal of maximizing

representativeness of the cohort, clinical accuracy of AKI, and feasibility in achieving the project goals. The data sources that will be used to ascertain information on these criteria may include electronic and paper medical records, other electronic databases, and patient interview or self-report.

- Inability to provide informed or surrogate consent.
- Died prior to the three-month study visit.
- Women or men who are incarcerated, institutionalized, or otherwise unable to participate in the study within a home, community, or clinical setting.
- Enrolled in an active interventional study at the three-month in-person study visit defined as receiving a study intervention at that visit regardless of the type of intervention (e.g., pharmacological, mechanical, lifestyle, educational, etc.).
- Women who are actively pregnant or breastfeeding.
- Prior chronic hemodialysis, peritoneal dialysis (lasting $\geq$ three months), or estimated GFR <15 ml/min/1.73 m^2 not receiving renal replacement therapy. The latter eGFR cutoff will be used given that any additional AKI in the setting of very low GFR will be difficult to detect and has unknown clinical significance.
- History of solid organ and/or hematopoietic cell transplants. Calcineurin inhibitors, the mainstay of anti-rejection treatment in transplant patients, can cause significant fluctuations in serum creatinine concentration that are both hemodynamic in the acute phase and can reflect renal fibrosis in the chronic phase.
- Acute glomerulonephritis. Glomerulonephritis is a unique phenotype of AKI that primarily involves the glomerulus rather than the renal tubules, and also has specific anti-inflammatory therapies. The acute glomerulonephritis may be diagnosed clinically or by biopsy. However, if the participant has a biopsy during the index hospitalization with results obtained after enrollment demonstrating a specific pathologic diagnosis not consistent with one of the exclusion criteria (e.g., a biopsy showing acute interstitial nephritis), the participant will remain eligible to continue in the study.
- Clinically significant urinary tract obstruction, confirmed by imaging, given that acute urinary obstruction is a reversible form of acute kidney injury that has a specific therapy.
- Hospitalization involving partial or total nephrectomy given that a rise in serum creatinine due to nephrectomy is not true “AKI” as approximately half of a person’s total nephron mass was acutely removed.
- History of multiple myeloma. The myeloma kidney resulting in acute renal failure is a completely different phenotype from typical “hospitalized AKI” and leads to very specific therapies (e.g., plasmapheresis).
- Hepatorenal syndrome. AKI in the setting of hepatorenal syndrome is a result of severe renal vasoconstriction, is nearly always a diagnosis of exclusion, and potentially has a therapy including but not limited to splanchnic vasoconstrictors, transjugular intrahepatic portosystemic shunt, and liver

transplantation.

- Metastatic cancer or systemic cancer receiving active treatment. These participants will be unable to allow complete evaluation of the long-term impact of an episode of AKI.
- Class IV heart failure prior to index admission. These participants have a very high short-term mortality rate and will be unable to allow complete evaluation of the long-term impact of an episode of AKI.
- Predicted survival of 12 months or less as determined by the participant's treating physician or Clinical Research Center Principal Investigator. These participants will be unable to allow complete evaluation of the long-term impact of an episode of AKI on various outcomes.
- AKI participants who remain hospitalized 90 or more days after the AKI episode as they would be unable to complete an outpatient three-month study visit following the identification of the AKI episode.
- ESRD at the time of the three-month study visit (three or more months of chronic hemodialysis or peritoneal dialysis).
- Unable to provide at least 1.5 mL of plasma for adults at the Inpatient visit.
- Unable to provide at least 3 mL of urine for adults at the Inpatient visit.
- Unable to provide at least 10 mL of blood for adults at the three-month visit.
- Unable to provide at least 20mL of urine for adults at the three-month visit.
- Unable to provide at least 1.6mL of urine for diaper wearers and 5mL of urine for non-diaper wearers for pediatric participants at the three-month visit and twelve-month visit.
- Unable to provide at least 0.175mL of plasma for pediatric participants at the twelve-month visit.

D.4. Calibration of Serum Creatinine Assay Results

Central to this study is the comparison of serum creatinine measurements observed before the AKI episode with serum creatinine measurements observed afterwards. Our current plan is to use these serial creatinine measurements to estimate the corresponding GFR's using the CKD-EPI[80] estimating equation which appears to be more reliable than the MDRD equation across the spectrum of actual GFR. We also note that if a better GFR estimating equation becomes available at the time of data analysis, we will use the newer equation assuming that necessary variables are available. Serum creatinine measurements before the AKI episode would be those obtained as part of routine clinical care of participants before they were enrolled into ASSESS-AKI. Serum creatinine measurements after the hospitalized AKI episode would be performed by the study Central Laboratory using blood samples obtained during scheduled ASSESS-AKI in-person study visits (see *Section D.13.3* for specimen ascertainment schedule).

This approach of using locally determined serum creatinine measurements to define "baseline" kidney function and a central laboratory for all sites to determine follow-up kidney function creates the potential for the introduction of systematic bias if there were serum creatinine measurement calibration differences between the local clinical laboratories and the study Central Laboratory. Numerous studies in the past few

years have highlighted this problem and stress the substantial magnitude of systematic error that can be introduced. For example, in a study by Murthy et al. of nationally representative laboratories, differences in serum creatinine results of up to 0.3 mg/dl are not uncommonly observed.[87] These systematic differences are propagated when differentially calibrated serum creatinine measurements are used to estimate GFR in equations such as the MDRD. Any fixed between-laboratory differences (e.g., Δ of 0.3 mg/dl) would have a disproportionately large impact among participants without significant serum creatinine elevation. In the Murthy study, the 95% confidence interval for the calibration difference was associated with a maximal range of error in GFR estimates from +4.6 to -18.1 mL/min/1.73 m^2 (+7.6 to -30.2%).[87]

In recognition of this problem, the National Kidney Disease Education Program has launched the Creatinine Standardization Program for clinical laboratories to establish and maintain isotope dilution mass spectrometry (IDMS) traceable calibrated serum creatinine assays.[88] These standardized serum creatinine values can then be used with equations such as CKD-EPI[80] to estimate baseline and follow-up GFR:

$$\mathbf{eGFR = 141 \times \min(S_{Cr}/\kappa,1)^{\alpha} \times \max(S_{Cr}/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018\ (if\ female) \times 1.159\ (if\ black)}$$

For the pediatric participants enrolled from the TRIBE-AKI, estimated GFR will be calculated using the Schwartz equation (Estimated GFR (mL/min/1.73 m^2) = 0.413 (Height, cm) / serum creatinine, mg/dL).[89] Because GFR physiologically increases from birth up until about 1 to 2 years, it is problematic to use eGFR as an outcome for comparing AKI versus non-AKI patients in groups of patients with varying ages. For example, a child may have a GFR of 50 ml per minute per 1.73m^2 at the age of 4 months old, which may be normal; however, at age 1.5 or 2 years old, this GFR would be low.

In order to account for the physiologic increase in GFR with age, we will express eGFR as percentile values according to age (similar to the way height is expressed in terms of percentiles). This will allow for meaningful comparison of AKI versus non-AKI children, regardless of age. This eGFR percentile method has been published in a manuscript by the TRIBE- AKI group [90] and used by this group to express baseline eGFR in several AKI manuscripts. [91] [92] The percentiles values were derived using data from 623 children without chronic kidney disease, who had nuclear medicine GFR testing performed.

Creatinine based eGFR will be the primary method for estimating GFR. However, eGFR will also be estimated using serum cystatin C (CysC-eGFR). Though SCr is the traditional method to estimate GFR, CysC may be a more accurate marker of GFR. Several CysC-eGFR equations exist or are being developed and validated. At the time of analysis, the CysC-eGFR equation which has been best validated will be used.

We naturally expect that all future central laboratory measurements in ASSESS-AKI will use IDMS standardized assays. It is critical in our study to try to minimize bias which could explain any observed association between an AKI episode and subsequent adverse outcomes.

Toward that end, the ASSESS-AKI Steering Committee had come to consensus agreement that only serum creatinine measurements from IDMS-standardized laboratories will be accepted for use in ASSESS-AKI analyses among its adult participants. The exception is that for the two TRIBE-AKI sites recruiting pediatric participants, we will accept serum creatinine measurements measured in the local hospital clinical laboratory before, during, and after surgery.

The pre-hospitalization (i.e., "baseline") serum creatinine values and the serum creatinine values obtained during the index hospitalization—used to define whether or not a patient has developed AKI in this study—will be measured at a local IDMS standardized laboratory. If an outside laboratory is using the Siemens/Dade Dimension or NOVA whole blood analyzer, the lab is not considered to be an IDMS-standardized laboratory. For example, as of January 28, 2008, all serum creatinine measurements (both inpatient and outpatient assays) performed at the Kaiser regional laboratory have been calibrated to IDMS. Participating sites within TRIBE and VALID will also rely on local IDMS calibrated assays to determine initial eligibility of individuals, with the exception of the two TRIBE-AKI pediatric surgery sites as noted above. Therefore, all participants enrolled into ASSESS-AKI should have directly comparable serum creatinine results before and after study follow-up is initiated.

The Steering Committee has proposed to split an obtained serum sample obtained at the three-month study visit in both AKI and non-AKI participants to measure serum creatinine concentration both at the local IDMS-standardized laboratory and at the ASSESS-AKI Central Laboratory. With the use of IDMS-standardized laboratories, there is little reason to believe that there will be a *systematic* difference in the serum creatinine concentrations measured between the local and central laboratory. However, IDMS standardization does not eliminate the effect of interfering substances which may have a greater impact when one serum creatinine measurement methodology is used rather than another. For example, it has been documented that dobutamine falsely reduces level of serum creatinine if the enzymatic method is used but not if the Jaffe method is used to measure serum creatinine.[93] Although there is little reason *a priori* to posit that these (very uncommon) causes of measurement error will lead to systematic differences in the serum creatinine measurements before and after an AKI episode or between those who do or do not suffer from AKI, our proposed split sample analysis from the three-month study visit will allow us to confirm this hypothesis.

D.5. Study Sample

D.5.1. Preliminary data on distribution of changes in serum creatinine in hospitalized patients from TRIBE, VALID, and Kaiser Permanente Northern California

D.5.1.1. *Preliminary Data from TRIBE-AKI*

Data below show the distribution of adult and pediatric patients enrolled through December 9, 2008 who met criteria for experiencing or not experiencing an AKI episode after cardiac surgery. (Tables 5 and 6)

Table 5. Number of adult patients enrolled in TRIBE-AKI with outpatient serum creatinine 2-365 days prior to admission meeting criteria for AKI and non-AKI.

Serum creatinine (SCr) change:	**Non-AKI** < 20% relative increase and ≤ 0.2 mg/dL increase	**AKI** ≥50% relative increase *or* ≥0.3 mg/dL increase	**AKI** Doubling of SCr	**AKI** Sustained (≥ 48 hours)
Prior CKD (eGFR <60 ml/min/1.73m^2)	55	50	6	38
No Prior CKD (eGFR ≥60 ml/min/1.73m^2)	145	78	11	38

Table 6. Number of pediatric patients enrolled in TRIBE to date with outpatient creatinine 2-365 days prior meeting criteria for AKI and non-AKI

Serum creatinine (SCr) change:	**Non-AKI** < 50% relative increase	**AKI** ≥ 50% relative increase	**AKI** Doubling of SCr	**AKI** Sustained (≥ 48 hours)
Prior CKD (eGFR <60 ml/min/1.73m^2)	66	36	18	12

D.5.1.2. *Preliminary Data from VALID*

As of February 1, 2009, 1,635 patients of the projected 2,550 patients have been enrolled. The study entry criteria selected for a severely ill patient population with an overall incidence of ALI/ARDS in the cohort of 25%. The incidence of sepsis is 41% and that of severe sepsis is 39%. In-hospital mortality is 19.6%.

According to the proposed ASSESS-AKI criteria, there is a high incidence of AKI in this cohort of approximately 27%. Of the first 1635 patients recruited, 1,442 were without ESRD or a history of renal transplant and had AKI status determined. Of these 1,442, 19% carried a diagnosis of CKD at the time of enrollment and 45% had medical information to indicate no CKD at the time of enrollment. In the remaining 36% of patients, there was no immediate medical information available to define presence or absence of CKD. Of the 277 patients with CKD, 52% developed AKI during hospitalization. Of the 650 patients without a known diagnosis of CKD, approximately 22% experienced a diagnosis of AKI.

D.5.1.3. *Preliminary Data from Kaiser Permanente of Northern California*

From January 2006 through June 2007, a total of 221,541 adult members were identified who were admitted to a Kaiser Permanente of Northern California hospital. After restricting this sample to the four Kaiser hospitals that are geographically close to the Kaiser Division of Research clinic facilities (*Oakland: 0 miles, San Francisco: 13.6 miles, Walnut Creek: 14.8 miles, and Hayward: 18.3 miles*), there were 65,001 members hospitalized during this time period. Among these patients, 28,910 had ≥ 2 outpatient serum

creatinine measurements within 24 months before hospital admission and ≥ 1 serum creatinine during the hospitalization. Applying the AKIN criteria for AKI (based only on serum creatinine changes), a total of 2,705 hospitalized individuals appeared to have an episode of AKI.

Selected baseline characteristics and in-hospital death rate for identified AKI participants are shown in Table 7.

Table 7. Characteristics of hospitalized Kaiser adult members who met AKIN criteria (Jan 2006-Jun 2007)

Characteristics	Subjects with AKI (N=2705)
Mean ± SD age, yr	69.3 ± 15.5
Women, N (%)	1350 (49.9)
Acute Kidney Injury Network (AKIN) Qualifying Criteria, N (%)	
Criteria 1 – absolute change ≥ 0.3 mg/dL (serial tests ≤ 48 hrs of each other)	1043 (38.6)
Criteria 2 – relative change from baseline ≥ 50% within first 48 hr of admission	1096 (40.5)
Both	566 (20.9)
Change in serum creatinine by criteria, Median (interquartile range)	
Criteria 1 – absolute change, mg/dL (N=1609)	0.44 (0.33 to 0.67)
Criteria 2 – relative (%) change from baseline (N=1662)	1.74 (1.58 to 2.15)
Diabetes mellitus, N (%)	1206 (44.6)
Died during index hospitalization, N (%)	335 (12.4)

Approximately 40% of AKI participants met AKIN criteria 1 or 2, with the remaining patients meeting both criteria. Persons with AKI were older, half were women, nearly half were diabetic, and 12% died before discharge—the latter likely reflecting the broader spectrum of AKI severity using the AKIN criteria. In addition, we know from prior studies in Kaiser that individuals who suffer from a severe acute or chronic condition have a disenrollment rate (not due to death) of <3% per year, so by the time that recruitment begins, there will be a significantly expected larger pool of readily available AKI patients.

Additional preliminary analyses show the number of qualifying individuals with and without AKI based on the ASSESS-AKI definitions detailed in *Section D.5.2* as well as comparisons of peak vs. baseline serum creatinine concentration in those with and without AKI stratified by pre-admission CKD status (Tables 8-10)

Table 8. Summary of the distribution of serum creatinine changes in hospitalized AKI and non-AKI subjects in Kaiser Permanente Northern California (January 2006 – June 2007)

AKI with Baseline eGFR ≥60	Mean (SD)	Median (IQR)	**Non-AKI with Baseline eGFR ≥60**	Mean (SD)	Median (IQR)
Baseline SCr	1.0 (0.2)	1.0 (0.8-1.1)	Baseline SCr	1.0 (0.2)	0.9 (0.8-1.1)
Peak SCr during hospitalization	1.9 (1.5)	1.5 (1.3-1.9)	Peak SCr during hospitalization	0.9 (0.2)	0.9 (0.8-1.1)
Delta SCr (Peak – Baseline)	0.9 (1.5)	0.5 (0.4-0.8)	Delta SCr (Peak – Baseline)	-0.02 (0.1)	0.0(-0.1-0.07)
AKI with Baseline eGFR <60			**Non-AKI with Baseline eGFR <60**		
Baseline SCr	2.4 (2.1)	1.6 (1.3-2.4)	Baseline SCr	1.6 (1.3)	1.3 (1.1-1.6)
Peak SCr during hospitalization	3.7 (3.0)	2.5 (1.9-4.0)	Peak SCr during hospitalization	1.4 (1.0)	1.3 (1.1-1.5)
Delta SCr (Peak – Baseline)	1.3 (1.6)	0.7 (0.4-1.4)	Delta SCr (Peak – Baseline)	-0.12 (0.40)	-0.07 (-0.20-0.05)

Table 9. Distribution of maximum relative increase in serum creatinine in persons with AKI. Results given as absolute numbers and row percentage.

RELATIVE INCREASE	50-59%	60-69%	70-79%	80-89%	90-99%	100-149%	150-199%	≥200%
Baseline eGFR ≥60 (N=1026)	257 (25.1)	152 (14.8)	99 (9.7)	82 (8.0)	52 (5.1)	166 (16.2)	67 (6.5)	151 (14.7)
Baseline eGFR <60 (N=1233)	285 (23.1)	180 (14.6)	135 (11.0)	112 (9.1)	72 (5.8)	209 (17.0)	97 (7.9)	143 (6.3)

Table 10. Distribution of maximum absolute increase in serum creatinine in persons with AKI. Results given as absolute numbers and row percentage.

ABSOLUTE INCREASE (mg/dL)	0.3-0.4	0.5-0.9	1.0-1.4	1.5-1.9	2.0-2.4	2.5-3.0	3.0-3.4	≥3.5
Baseline eGFR≥60 (N=1869)	901 (48.2)	601 (32.2)	150 (8.0)	66 (3.5)	37 (2.0)	24 (1.3)	24 (13)	66 (3.5)
Baseline eGFR<60 (N=3236)	1005 (31.1)	1053 (32.5)	415 (12.8)	224 (6.9)	143 (4.4)	93 (2.9)	64 (2.0)	239 (7.4)

Overall, these data demonstrate the large number of persons who appear to have suffered an episode of hospitalized AKI and the broad spectrum of AKI severity. In addition, there will be a substantially larger source population of non-AKI subjects to recruit from into ASSESS-AKI.

D.5.2. Operational Definition of AKI for Enrollment into ASSESS-AKI

As described previously in *Section B.2*, we recognize the limitations of the most recently proposed definitions for AKI, which are based only on changes in serum creatinine concentration and/or urine output. However, despite enthusiasm for potentially more sensitive and specific novel serum and urine biomarkers, to date, they have not been sufficiently validated as better measures of AKI or subsequent prognosis than serum creatinine-based criteria. A major goal of ASSESS-AKI is, in fact, to provide key insights into the prognostic value of novel biomarkers. Therefore, AKI will be operationalized as follows which is anticipated to capture a broad spectrum of kidney injury.

D.5.2.1. *Adult definition of presumed AKI*

For adult (age ≥18 years) participants, AKI will be defined as ≥ 50% relative increase OR absolute increase ≥ 0.3 mg/dL (27 umol/L) in peak inpatient serum creatinine compared with baseline outpatient serum creatinine.

For patients with recurrent episodes of AKI during the index hospitalization to be eligible to be enrolled at any episode after the first detected one, they have to meet criteria for non-AKI (ie, minimum of two serum creatinines in between and ≤0.2 mg/dL change above baseline) between episodes.

D.5.2.2. *Pediatric definition of presumed AKI*

For pediatric (age greater than one month and less than 18 years) participants, AKI will be defined as ≥ 50% relative increase in peak inpatient serum creatinine compared with baseline outpatient serum creatinine.

D.5.2.3. *Spectrum of Severity of AKI and Reasons for Variation from AKIN Criteria*

To enhance the likelihood of enrolling an adequate number of adult participants with more severe AKI, we have an enrollment target of at least one third of AKI participants having ≥ 100% relative increase in serum creatinine. To increase the likelihood of having an adequate number of adult participants with AKI due to causes other than rapidly reversible pre-renal azotemia, we have an enrollment target of at least one third of AKI participants who meet AKI criteria lasting ≥ 48 hours. We anticipate that there will be overlap in these two subgroups.

Since the primary aim of this study is to determine whether or not AKI leads to incident CKD or more rapid progression of CKD, a critical consideration for this study is the pre-hospitalization baseline creatinine. Since there is no clear definition for baseline creatinine in the AKIN definition of AKI, we did not incorporate the timing element (i.e., requiring a rise in serum creatinine within 48 hours). Rather than mandating a change within 48 hours of hospitalization, we chose to mandate a change from a well-established baseline pre-hospitalization creatinine. We did not incorporate the urine output criteria from the AKIN classification scheme because the Steering Committee was concerned about the quality of the primary data on documented total fluid intake and urine output, especially in non-ICU patients who are likely to not have indwelling urinary catheters. Furthermore, there was concern that incorporating the urine output criteria for AKIN might overly enrich our cohort for patients with prerenal azotemia.

D.5.3. Non-AKI Participant Selection

Given the proposed matched parallel cohort design, we will identify and enroll a sample of hospitalized patients who did not appear to suffer an AKI episode and who are matched on a minimal set of key confounding characteristics (see *Section D.6*).

D.5.3.1. *Adult Non-AKI definition*

For adult participants, non-AKI status will be defined as < 20% relative increase AND absolute increase ≤ 0.2 mg/dL (17umol/L) in peak inpatient serum creatinine compared with baseline outpatient serum creatinine.

D.5.3.2. *Pediatric Non-AKI definition*

For pediatric participants, non-AKI status will be defined as < 50% relative increase in peak inpatient serum creatinine compared with baseline outpatient serum creatinine.

D.6. Matching Criteria for AKI and non-AKI participants

D.6.1. AKI and Non-AKI Matching Ratio and Timing

Each CRC will pursue a minimum of a 1:1 ratio for AKI: Non-AKI participant matching for those enrolled in long-term follow-up. Vanderbilt will enroll 250 AKI and 250 matched Non-AKI participants into long-term follow-up. The University of Washington will recruit a minimum of 200 AKI and 200 matched Non-AKI participants into long-term follow-up. Kaiser will enroll 156 AKI and 156 matched Non-AKI participants into long-term follow-up. Yale will recruit 200 AKI participants and 200 non-AKI participants from the parent TRIBE-AKI study, with a current plan of 300 adults and 100 children. The maximum ratio is 1:3 for AKI: Non-AKI participant matching. More than one AKI participant may not be matched to one non-AKI participant. Once enrolled as either an AKI or non-AKI participant, the participant may not switch groups. A matching non-AKI participant will be targeted to be enrolled within 18 months after an AKI participant is enrolled into the long-term follow-up (i.e., defined as completion of the 3-month study visit). Recruitment of a match is permitted in the opposite manner as well, i.e., a matching AKI participant will be targeted to be enrolled within 18 months after a non-AKI participant is enrolled into the long-term follow-up, See discussion in *Section D.6.4* below for rationale of proposed matching approach. If no match can be found, the AKI or non-AKI participant may continue in the study as a singlet.

D.6.2. Mandatory Matching Criteria

AKI and non-AKI participants will be matched for the following three variables:

- CRC (Kaiser, TRIBE-AKI, VALID, and University of Washington)
- Baseline chronic kidney disease status (yes, no) using CKD-EPI[80] estimated GFR threshold of < 60 or ≥ 60 ml/min/1.73 m^2

- Age group (adult, pediatric)

D.6.3. Additional Matching Considerations

To further reduce confounding, we will attempt to further match AKI and non-AKI participants for the following prioritized set of participant characteristics (Note: for pediatric *participants being enrolled through TRIBE, no additional matching will be conducted because all non-AKI participants will be enrolled*):

- Prior cardiovascular disease (non-CVD, CVD)
- Prior diabetes mellitus (non-DM, DM). Diabetes mellitus will defined as meeting one or more of the following criteria consistent with American Diabetes Association criteria[94]:
  - Preadmission physician diagnosis of diabetes mellitus.
  - Participant self-report or medical record that participant is currently on any oral or injectable hypoglycemic agents (prior to index admission or upon initial follow-up visit)
  - Without a documented history in patients with suspected type 2 diabetes, the diagnosis can also be based on a fasting plasma glucose ≥ 126 mg/dL or symptoms of hyperglycemia (polyuria, polydipsia, and unexplained weight loss) and a casual outpatient plasma glucose ≥ 200 mg/dL prior to or upon follow-up blood work (one value of each criterion from separate days or two separate values of one of the criterion from separate days). Fasting is defined as no caloric intake for at least eight hours. Casual is defined as any time of day without regard to time since the last meal.[94] No glucose measures during the index hospitalization will be used given that acutely ill patients can experience reversible hyperglycemia that is not due to underlying diabetes.
- Category of baseline estimated GFR (15-29, 30-44, 45-59, 60-89, 90-150 ml/min/1.73 m^2)
- Baseline Adult age category (18-39, 40-49, 50-59, 60-69, 70-79, 80-89 years)
- Hospital location where AKI episode occurred (e.g., non-ICU, ICU)

A point system will be applied to assess the level of matching according to the secondary matching criteria. The points assigned for matching a non-AKI participant to an AKI participant range from 0 to 100 in the following manner:

1. Prior cardiovascular disease (non-CVD, CVD) – 30 points if the AKI participant and the non-AKI participant are within the same category, 0 points if the AKI participant and the non-AKI participant are not in the same category.
2. Prior diabetes mellitus (non-DM, DM) – 25 points if the AKI participant and the non-AKI participant are within the same category, 0 points if the AKI participant and the non-AKI participant are not in the same category.
3. Baseline eGFR categories (15-29, 30-44, 45-59, 60-89, 90-150) – 20 points if the AKI participant and non-AKI participant within the same category, 10 points if the AKI participant and the non-AKI participant are one category apart, and 0 points if the AKI participant and the non-AKI participant are two categories apart.
4. Age categories (0-17, 18-39, 40-49, 50-59, 60-69, 70-79, 80-89) – 15 points if the AKI participant and non-AKI participant within the same category, 10 points if the AKI participant and the non-AKI participant are one

category apart, 5 points if the AKI participant and the non-AKI participant are two categories apart, and 0 points if the AKI participant and the non-AKI participant are three or more categories apart.

5. Hospital location (non-ICU, ICU) – 10 points if the AKI participant and the non-AKI participant are within the same category, and 0 points if the AKI participant and the non-AKI participant are not in the same category.

D.6.4. Summary of AKI and Non-AKI Participant Selection Approach

Figure 10 below summarizes the overall approach to selection of AKI and non-AKI participants and timing for the planned enrollment into the long-term ASSESS-AKI follow-up (Figure 10). This approach will be operationalized at each of the CRC's.

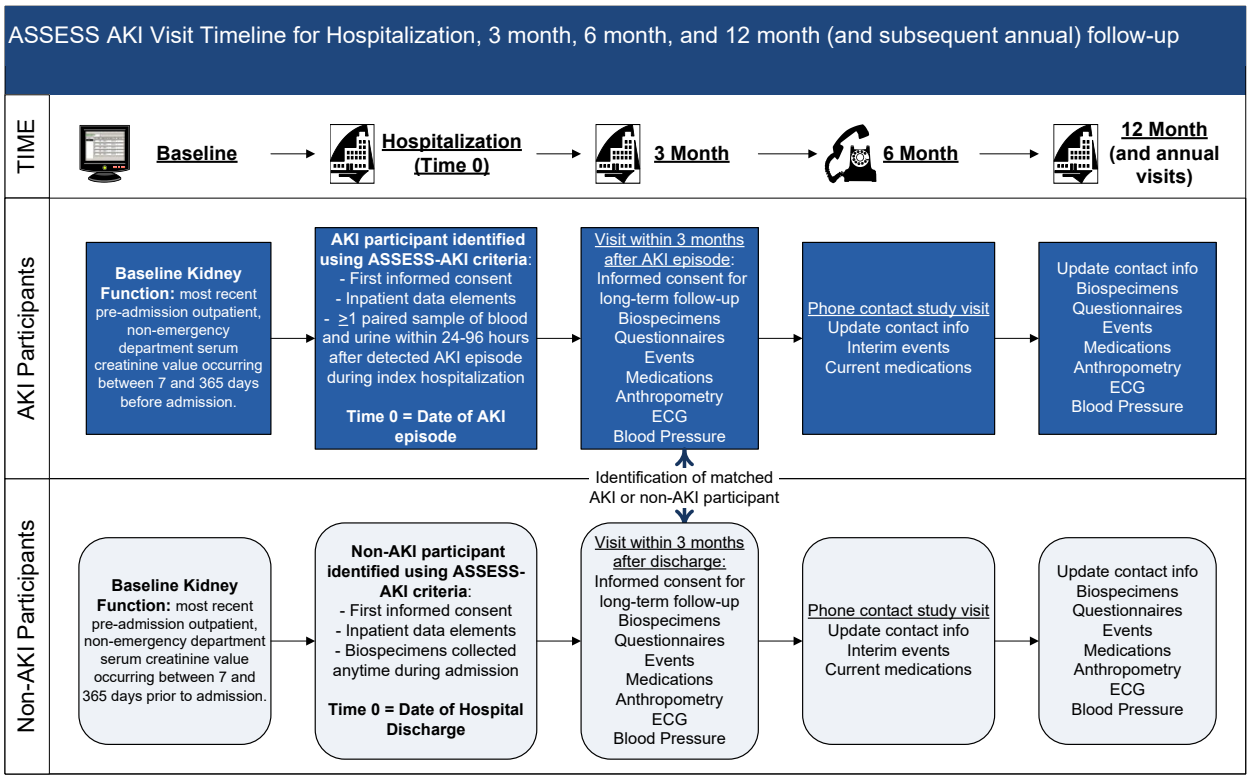


Figure 10. Summary of Identification and Enrollment Approach for AKI and Non-AKI Participants.

This consensus approach is based on the main principle that the study design needs to support the primary goals of the study within the available resources. The proposed approach provides a more optimal and rigorous design for examining long-term outcomes associated with AKI vs. no AKI among hospitalized patients while still allowing for evaluation of the link between occurrence of AKI and very short-term clinical outcomes (e.g., cardiovascular event, initiation of dialysis). We address next the rationale for this enrollment and matching strategy:

There were several reasons why we propose to match non-AKI participants based on the subset of AKI participants who completed the three-month study visit:

- While we are interested in the very short-term outcomes (i.e., within three months of an AKI episode), the main goal of Aim 1 is to examine the long-term renal implications (both incident CKD, progression of CKD, ESRD, etc.) among persons who survive an AKI episode since this is a primary unanswered question in the field. Toward that end, based on currently available resources and power calculations (see *Section E*) for our primary outcomes, our target is to include 800 AKI and 800 matched non-AKI participants who officially enrolled into the long-term study which is defined as completing the three-month study visit. This approach will provide for more optimal matching of key characteristics that might confound any observed association between an episode of AKI and subsequent *long-term* outcomes as it focuses on any differences in characteristics of survivors of a hospitalization involving AKI for whom long-term outcomes are most relevant.
- The choice for using a matching approach itself was based on the concern that a sample size of 800 AKI and 800 non-AKI subjects may provide adequate power to detect only large effect sizes and that we may not be able to adequately control for residual confounding using traditional statistical case-mix adjustment methods because of the sample size that could be obtained within currently available resources.
- It is also important to note that time zero is the date of the detected AKI episode that prompted initial enrollment which includes obtaining at least one set of blood and urine specimens up to 96 hours after the AKI episode. For non-AKI participants, time zero is the date of hospital discharge since they will not have any relevant event during the index hospitalization to anchor to and will likely have relatively short hospital lengths of stay.

What are the implications for matching subjects who have completed a three-month visit to subjects who have not completed a three-month visit?

There are several implications to choosing a design that matches on subjects who do not make it to the three-month visit. They revolve around efficiency, ability to ensure adequate matching for controlling confounding and currently available resources.

- We already know from multiple published studies that patients who suffer an AKI episode are more likely to die during the index hospitalization or shortly thereafter (see *Section B.3*). There will be an expected higher censoring rate in the AKI participants due to death within the first three months after the AKI episode, which will preclude their participation in long-term follow-up and for whom long-term changes in kidney function and related outcomes are not relevant. Therefore, using the profile of all AKI participants (rather than the subgroup who attend the three-month study visit) for matching purposes will lead to suboptimal matching and control of key confounders when examining long-term renal, cardiovascular, and other outcomes of interest.
- In the present study design, we know that a non-trivial fraction of participants who are initially enrolled during the hospitalization will not have a three-month study visit (due to death, refusals, development of exclusion criteria or loss to follow-up), so >800 persons with and without AKI will need to be contacted during the index hospitalization in order to reach the target goal of 800 AKI and 800 non-AKI participants who complete a three-month study visit. Given this, recruitment of subjects using matching based on only the in-hospital recruitment status will lead to a significant excess of un-matched pairs who complete the three-month study visit. This is inefficient for trying to answer the main goal of Aim 1 and also costly given that we would need to enroll a significantly larger number of participants beyond the target of 800 AKI and 800 non-AKI to ensure that we will have enough 1:1 matched AKI and non-

AKI pairs who are able to initiate long-term follow-up.

Does our current matching approach prevent us from examining the first three months of follow-up for outcomes?

- Even though a standard cohort design (e.g., enrolling all hospitalized patients) would be more comprehensive to examine very short-term outcomes between AKI and non-AKI participants, our study design will still allow us to examine both short-and long-term outcomes after AKI. As noted above, the start of follow-up (i.e., time zero) for AKI participants is the time of their detected AKI episode and follow-up begins at hospital discharge for non-AKI participants. For both groups, we will have at least one set of biospecimens as well as relevant inpatient data, and we will be able to characterize their outcomes after time zero. Even though some participants will be matched to participants who completed the three-month visit, we will have in-hospital data and biospecimens on both AKI and non-AKI participants initially enrolled in the hospital, and the only difference is that we would anticipate a smaller rate of death or loss to follow-up as a cause for why non-AKI participants did not make it to the three-month study visit. Therefore, we will need to select several matched non-AKI subjects per AKI subject to ensure that we have at least one that completes the three-month study visit.
- Using data only from the in-hospital data collection process, we will be able to model the risk of different outcomes during the first three months after initial enrollment and the covariates included in those models will be limited to those obtained during the index hospitalization. These analyses can be done among all AKI subjects for which we obtained in-hospital consent as well as all non-AKI subjects for whom we obtained in-hospital consent, and we can still control for potential confounding in our current design even if the matching is imperfect since we'll have data on a variety of relevant covariates obtained during the index hospitalization enrollment process among all subjects, including those that do not make it to the three-month study visit.

D.7. Type of AKI

D.7.1. Assessment of the presumed type of AKI

Study nephrologists at each CRC will review selected inpatient information including renal consultation notes and discharge summaries for each enrolled AKI participant to conduct a clinical evaluation about the episode of presumed AKI. This subset will form the basis of secondary statistical analyses.

D.7.2. Additional categorizations by presumed nature of kidney injury

The following three categories will be used to assign a presumptive cause of AKI:

- Acute tubular necrosis (ATN)
- Prerenal azotemia
- Other specify /Unknown

D.7.3. Process for assigning presumed type of AKI

Following hospital discharge and by the time of the three-month study visit, we will review relevant medical records (e.g., renal consultation notes, discharge summary) for all AKI participants to collect information on a diagnosis of ATN, prerenal azotemia, and/or other/unknown AKI (or "acute renal failure"). For participants who experience ATN during the index hospitalization, even if there are other contributing etiologies (e.g., prerenal azotemia), they will be classified as ATN.

However, experience from TRIBE-AKI has shown that even when inpatient medical records were reviewed by a group of experienced nephrologists, there was difficulty in achieving consensus on the presumed type of AKI (C. Parikh, personal communication). In addition, as noted previously, among patients meeting AKI criteria in typical clinical practice settings within Kaiser, fewer than 33% of the discharge summaries were coded for AKI using available ICD-9 codes.

D.8. Recruitment Approaches

D.8.1. TRIBE-AKI

Yale will recruit 200 AKI participants and 200 non-AKI participants from the parent TRIBE-AKI study, with a current plan of 300 adults and 100 children. On day 3 or 4 of hospitalization, each subject will be screened by research personnel for feasibility of long-term follow-up and asked for permission for future contact. Information on two additional contacts names/numbers will also be obtained at this time. If the subject agrees to long-term follow-up, the following steps will be initiated.

(1) Every month, a Co-Investigator will query the "TrialDB" on-line database for all participants with AKI and all eligible non-AKI participants matched for the pre-specified criteria with the index participant with AKI.

- Eligible participants with non-AKI will be "ranked" for each in order from best match to worst match for each participant with AKI in the new time period.

(2) Materials to be mailed to all potential AKI and non-AKI participants considered eligible for long-term follow-up will be prepared approximately one month before the three-month visit. The mailing will include a thank you letter, trifold flyer containing explanation of the long-term study, and a "Certificate of Appreciation."

(3) One week after the mailing, research personnel at each site within TRIBE-AKI will call eligible participants.

- All adult participants with AKI will be contacted, unless targets for spectrum of severity are lagging (see *Section D.5*), in which case only higher spectrum of severity AKI participants will be contacted and enrolled.
- Adult participants will be contacted in order from highest number of matching criteria to lowest until the participant is secured for a three-month visit.
- Participants will be given a choice of follow-up at the research clinic or in their home.

- At the three-month visit, study personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.
- All children, of both AKI and non-AKI status, who agree to long-term follow-up, will be identified, contacted, and followed.

D.8.2. VALID

Vanderbilt will recruit 250 adult AKI participants and 250 matched adult non-AKI participants from the ICU's and hospital floors at Vanderbilt and the local VA Medical Center (Tennessee Valley Healthcare System – Nashville Campus); including but not limited to those enrolled in VALID. Hospitalized patients will be screened daily. Patients meeting inclusion/exclusion criteria outlined in the protocol will be enrolled into the proposed study based on assessment of AKI versus non-AKI status. Serum creatinine data will be extracted from the electronic medical record to assess for the presence of AKI.

Once potentially eligible participants are identified:

- Research personnel will enroll subjects into the study and a copy of the informed consent will be provided.
    - As critically ill patients are often temporarily mentally disabled due to the nature of their underlying illness or receiving sedative medications for their safety and comfort, surrogate consent will be obtained for patients initially if the patient cannot provide informed consent. If patients are initially unable to consent and become able to consent, then informed consent will be obtained.
- If AKI participants do not meet the criteria for severe AKI (≥ 100% relative increase in peak inpatient serum creatinine compared with baseline outpatient serum creatinine, or receipt of dialysis), then the AKI participants will be withdrawn from the study as screen fails.
- If participants are not dialysis-dependent at discharge, continue to meet eligibility criteria, and agree to participate in the study, participants will be invited to attend the three-month study visit.
- Participants will be given a choice of follow-up at the research clinic or in their home.

D.8.3. Kaiser Permanente Northern California

Kaiser will recruit 157 adult AKI participants and 157 adult matched non-AKI participants from up to four Kaiser medical centers as described below:

For AKI participants:

- Research personnel will go to each recruiting hospital and after confirming access to the AKI participant, obtain written consent from the participant to complete a short questionnaire, to obtain a single non-fasting blood specimen and random urine sample, and to confirm the participant's agreement to be contacted within the next 30 days to discuss the study further.
- Within 30 to 45 days after hospitalization, a follow-up letter from the CRC PI will be sent to each AKI participant enrolled during the acute hospitalization to introduce the long-term study protocol.

- One week after sending the letter, research personnel will call the AKI participant to screen for remaining eligibility and to schedule the three-month visit.
- At the three-month visit (conducted at a central research clinic in Oakland), research personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.
- Research personnel also will review the consent at the 12-month follow-up visit to reinforce the schedule and study protocol with the participant.

For non-AKI participants:

- After an AKI participant successfully completes a three-month study visit, research personnel will identify a pool of up to ten possible matched non-AKI participants who are hospitalized within a recent time frame of the enrolled AKI participant.
- Prior to hospital discharge, research personnel will go to each recruiting hospital and after confirming access to the potential non-AKI participant, obtain written consent from the non-AKI participant to complete a short questionnaire, to obtain a single non-fasting blood specimen and random urine sample, and to confirm the participant's agreement to be contacted within the next 30 days to discuss the study further.
- Within 30 to 45 days after hospitalization, a follow-up letter from the CRC PI will be sent to each non-AKI participant enrolled during the acute hospitalization to introduce the long-term study protocol.
- One week after sending the letter, research personnel will call the non-AKI participant to screen for remaining eligibility and to schedule the three-month visit.
- At the three-month visit, research personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.
- Research personnel also will review the consent at the 12-month follow-up visit to reinforce the schedule and study protocol with the participant.

D.8.4. University of Washington

The University of Washington will recruit 200 adult AKI participants and 200 matched adult non-AKI participants from the ICU's at Harborview Medical Center. Patients in the trauma, surgical, and medical ICU's will be screened daily for inclusion/exclusion criteria. The CRC will seek IRB permission to initiate collection of samples before consent has been obtained. This will allow the CRC to enroll patients who are too ill to provide consent but are without local surrogates. If consent is not obtained, these samples will be destroyed.

Patients/surrogates will be approached for possible consent into the ASSESS-AKI study on day 1 of their hospitalization. Upon this initial contact, the CRC will ask for consent for participation in a short questionnaire, collection of study samples, and permission for further contact for long term aspects of the study. The CRC will obtain additional contact names/numbers as well. The CRC anticipates two possible scenarios for the consent process of study subjects.

Cohort 1:

1) For those patients with a pre-hospitalization creatinine within the past 365 days documented in the medical record, immediate enrollment into the study can occur. Sample collection will be initiated and serum creatinine data will be extracted from the electronic medical record to assess for the presence of AKI.

2) Patients in whom surrogate consent is obtained during hospitalization will need to provide informed consent by the three-month visit and efforts will be made to obtain consent before hospital discharge. Patients unable to provide informed consent by the three-month visit will be ineligible for the longitudinal study.

3) The CRC anticipates that given the proposed matched parallel cohort design, the CRC will be enrolling both AKI participants and non-AKI participants and will ultimately be matched on a minimal set of key confounding characteristics per study protocol.

Cohort 2:

1) For patients without a pre-hospitalization creatinine, the CRC will ask for consent as noted above and will additionally ask for signatures on a Release of Medical Information form so that primary care or referral providers may be contacted for potential creatinine values within the past year. If obtained, verification that creatinine values were obtained from IDMS-standardized laboratories will occur. Sample collection will be initiated. If creatinine values are unable to be determined, these subjects will not be contacted for the follow up portion of the study.

2) If surrogate consent has been obtained, subjects will be re-consented before discharge and concurrently approached for consent to place their samples and data in the University of Washington KRI Data and Biosample Repository.

Within one to three weeks following discharge, materials will be mailed to all potential AKI and non-AKI participants enrolled during the acute hospitalization to introduce the long term follow up protocol. The mailing will include a thank you letter plus a flyer containing explanation of the long-term study. One week after mailing, research personnel will call eligible participants to answer potential questions, screen for remaining eligibility, and invite them to attend the three-month study visit.

At the three-month visit (conducted at the University of Washington KRI facilities and laboratory or in patient home), research personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.

D.9. Screening and Enrollment Timing and Diversity

D.9.1. Screening and enrollment of AKI participants

AKI participants will be identified first as described in *Sections D.5-D.8* above and enrolled into the long-term follow-up at an outpatient study visit completed at three months after the AKI episode is recognized. Within 18 months of a completed three-month study visit for each AKI participant, at least one matched non-AKI participant will be targeted for study enrollment.

D.9.2. Screening and enrollment of non-AKI participants

Non-AKI participants will be identified first as described in *Sections D.5-D.8* above and enrolled into the long-term follow-up at an outpatient study visit completed at three months after hospital discharge. Within 18 months of a completed three-month study visit for each non-AKI participant, one matched AKI participant will be targeted for study enrollment.

D.9.3. Gender and racial/ethnic representation

ASSESS-AKI will target recruitment of a study sample with broad gender and racial/ethnic diversity that is representative of the AKI population in the U.S.

D.10. Participant Follow-Up Schedule and Types of Contact

Enrolled AKI and non-AKI participants will be contacted at 3, 6, 12, 18, 24, 30, 36, 42, and 48 months to obtain systematic information on relevant exposures and outcomes. For participants who agree to sign a new consent form, the follow up has been extended beyond the original planned period to include up to 96 months.

The last contact with participants enrolled at Yale, Vanderbilt, and Kaiser Permanente Northern California CRCs was on or before November 30, 2017. University of Washington's last contact was January 24, 2019.

D.10.1. In-Person Study Visits

The 3-, 12-, 24-, 36-, 48-, 60-, 72-, 84- and 96-month contacts will be in-person visits. The target window for the first visit will be ± four weeks and for subsequent visits will be ± six weeks. For AKI participants, the initial outpatient study visit will completed three months after the AKI episode is recognized. For non-AKI participants, the initial outpatient study visit will be completed three months after hospital discharge. Pending future financial support, additional annual follow-up visits will be pursued.

D.10.2. Telephone Calls

The 6-, 18-, 30-, 42-, 54-, 66-, 78-, and 90-month contacts will consist of telephone calls, lasting an estimated 10 to15 minutes, to collect relevant outcome and medication use data and to update contact information.

D.11. Participant Retention and Tracking

To maximize participant retention, we will employ several successful strategies that have been employed in various prospective cohort studies, including the CRIC Study,[95] AIDS cohort study,[96] Nurses' Health Study,[97] and the Women's Health Initiative Clinical Trial and Observational Study.[98] Use of some of these strategies has yielded a long-term success rate of >90% at three years in the CRIC Study,[95] 89% at 9.5 years in the Multicenter AIDS Cohort study,[96] 90% success rate at eight years in the Nurses' Health Study,[97] and 97% at ten years in the Women's Health Initiative Study.[99]

These include having a single Project Coordinator as the primary contact who will develop a long-term relationship with participants to enhance attendance at follow-up visits. The following additional tracking and retention strategies will be used to augment this relationship and to maintain long-term contact with and follow-up of study participants:

- Attempts to obtain Social Security Number information that will be used for ascertaining vital status among participants who are lost to follow-up. It will be optional for participants to provide this information.
- Phone and address listings for subjects and contacts will be updated at each interaction (visits/phone).
- Personalized letters and notes from the PI and Project Coordinator will be sent.
- Study newsletters (providing information on the study progress and results, along with general and kidney-specific health messages) will be mailed. Personalized birthday and holiday greeting cards will be sent.
- Approximately two to four weeks prior to the time for the follow-up visits, a phone call will be placed to the participant to schedule the date and time of the appointment.
- A reminder letter with the date, time, and location of the visit may be sent to the participant immediately after the visit is scheduled.
- Proxy interviews to collect primary outcomes will be conducted if the participant is deceased or has diminished cognitive functioning.

In addition, there will be site-specific efforts to enhance participant retention.

Yale. Additional strategies include the following: (1) participants who will be enrolled in the parent study will also be consented to this planned long-term study simultaneously; (2) a thank you letter, along with a certificate recognizing their participation, and a tri-fold pamphlet with study name, logo, information, study processes, and contact numbers and photos of the investigators and coordinators will be sent four weeks after discharge from the hospital; (3) research visits will be offered to be conducted in the participants' homes for participants who cannot drive to the research unit.

Kaiser. Two additional strategies will be employed including (1) providing an annual *Renal Health Assessment* by a Kaiser Nephrologist who will review relevant clinical and laboratory tests and provide any guideline-based recommendations; and (2) monthly review of the Kaiser membership list to determine membership status of enrolled participants.

Vanderbilt. Additional strategies include the following: (1) a thank you letter and a tri-fold pamphlet with study name, logo, and information; (2) study processes, and contact information is sent to the patient after discharge from the hospital and enrollment in the study; (3) research visits will be offered in the participants' homes for participants who cannot drive to the research unit.

We will also employ the following strategies to trace hard to find and lost participants:

- Extended search will be initiated for those who cannot be reached, including contacts with personal contacts and the primary care physician.

- US postal service will be contacted for current address (National Change of Address system).
- Use of reverse telephone directories and other online reference data sources.
- National Death Index[100] will be searched for the occurrence and potential cause of death among participants who are considered lost to follow-up. This will be facilitated by requesting collection of social security number information from participants upon enrollment into the long-term study. It is recognized that there is a significant temporal delay in the availability of data from the National Death Index, so Social Security Administration vital status files[101] will be another complementary source given that it is updated quarterly.

Washington. Two additional strategies include the following: (1) a thank you letter and pamphlet with study name, logo, and information including contact numbers and photos of investigators and coordinators will be sent post discharge; (2) will offer to coordinate research visits with return physician visit appointments if patient prefers, will offer parking validation, and also the choice for the visit to take place in the participants' homes for their convenience.

D.12. Participant Withdrawal

It is anticipated that over the course of time, a small number of ASSESS-AKI participants may withdraw from the study. This may occur officially by formal written notification from the participant to a CRC Principal Investigator, or unofficially when a participant cannot be reached via the usual methods of contact and in whom death cannot be confirmed. Every effort will be made to ensure high rates of long-term retention and to acquire complete data on all participants (see *Section D.11*).

Participants, who relocate to an area where they can no longer travel to a CRC, will be asked if study personnel may contact them annually for a telephone contact to complete the in-person forms. Centers may offer inducements to participants who drop-out or relocate in the form of additional travel reimbursement in return for their continued participation.

D.13. Data Sources and Study Data Collection

D.13.1. Sources of Information

D.13.1.1. *Medical Records*

Medical records will be examined to confirm the exact date for objective events (MI, hospitalization), but there will be those events for which the exact date will be unknown based on either missing or incomplete information.

To enhance efficiency of data collection, we will take advantage of information within electronic health records that have been implemented at CRCs and their sub-sites. Table 11 summarizes the types of relevant data types that are presently available

Table 11. Summary of elements contained with electronic health records at each ASSESS-AKI CRC

	Demo-graphics	Vital Signs	Medications	Input/ outputs	Laboratory and Pathology Results	Radiology Results	Operative Reports	Discharge Summaries, Diagnoses and Procedures	Ambulatory Visit Diagnoses and Procedures
TRIBE									
Yale	X		X		X	X	X	X	
London	X		X		X	X	X	X	
Cincinnati	X	X	X	X	X	X	X	X	X
Montreal	X		X		X	X	X	X	
VALID									
Vanderbilt	X	X	X	X	X	X	X	X	X
Kaiser									
All sites	X	X	X		X	X	X	X	X
UW									
All sites	X	X	X	X	X	X	X	X	X

Relevant data that are not retrievable from electronic health records will be abstracted from paper medical records.

D.13.1.2. *Local and Central Laboratories*

While it is expected that nearly all laboratory tests will be performed through the University of Minnesota as the ASSESS-AKI Central Laboratory, depending on the final set of laboratory tests that will be performed as part of the core protocol, certain assays may be required to be conducted through local laboratories that support CRCs (e.g., complete blood count). Systematic information on specific assay details will be obtained for all locally performed tests to ensure comparability of accuracy and reproducibility of results across CRCs which will all use different local laboratories.

D.13.1.3. *Central Reading Centers*

For adult participants, we will obtain a 12-lead electrocardiogram at the in-clinic V3M baseline study visit and every subsequent in-clinic study visit. Acceptable ECGs include those done by research personnel and those done in clinical ECG laboratories or available through clinical paper or electronic medical records.

- Baseline Visit ECG
    - All adult sites should make every effort to get an ASSESS-AKI ECG (either through their research center or send the participant to the ECG lab), or retrieve a clinically-obtained ECG from the medical records.
    - For participants who have already completed the V3M visit but in whom research personnel did not obtain an ECG at that time, clinical records from the site should be reviewed and a clinical ECG most proximate and preceding the V3M visit should be obtained. This ECG could be obtained during the V0 hospitalization or at an outpatient visit or during hospitalization that is not more than 365 days prior to the V0 hospitalization. Preferably, an ECG nearest to the V0 hospital discharge date would be available and would be acceptable.

- Baseline ECG is defined as an ASSESS-AKI ECG at V3M, a non-ASSESS ECG obtained during the V0 hospitalization, or at an outpatient visit or hospitalization that is no more than 365 days prior to the V0 hospitalization.
- Baseline ECGs should be obtained for those who withdraw at or after V3M without a post-baseline ECG.
- Baseline ECGs should be obtained for those who withdraw at or before V24M without a post-baseline ECG

- Post-Baseline Visit ECG
  - In-center visits – all adult sites should obtain an ASSESS-AKI ECG for all visits (either through their research center or send the participant to the ECG lab), or retrieve a clinically-obtained ECG from the medical records within the follow-up window.
  - Home visits/Phone visits in lieu of in-center visits – all adult sites should attempt to obtain a mobile ECG. If a mobile ECG is not possible, the coordinator will know after the next phone contact if there was a hospitalization(s) or ER visit (P1_EVENTS, Q1000 = 1) and will ask if s/he has had an ECG during the hospitalization or within the last six months. If the participant does not know if an ECG was completed, a quick search of the local EMR should be completed. After completing the HOSP_EVAL for the hospitalization(s), the coordinator will request an ECG as part of the medical records request. If an ECG is not available from the medical records, the coordinator shall contact the provider where an ECG was completed within the last six months; this can be a hospital, clinic, or physician office. If no, the ECG will be considered missing.
  - Post-baseline visit ECG is defined as any ECG (ASSESS or non-ASSESS) obtained after V3M.
  - Only one ECG should be obtained annually after the post-baseline ECG, and it should be collected at the annual visit or a hospitalization most proximate after the scheduled visit.

Ideally, to provide a systematic comparison at the start of the study, at least one ECG obtained before or during the index hospitalization will be obtained for each participant and stored locally at each CRC.

Prior to the beginning of participant recruitment into ASSESS-AKI, Wake Forest (EPICARE) was identified as the ASSESS-AKI Central ECG Reading Center that will electronically receive digital electrocardiograms and provide a systematic evaluation for relevant electrocardiographic findings.

D.13.2. Index Hospitalization Data Collection

The following sections provide a brief description of the data elements that will be collected during the index hospitalization for both AKI and non-AKI participants.

D.13.2.1. *Demographic characteristics*

This will include the following variables:

- Date of birth (mm/dd/yyyy; Yale London/Ontario: mm/yyyy)
- Self-reported gender (male, female, other, unknown)

- Self-reported race (white/European, black/African American, Asian, Native Hawaiian or Pacific Islander, Native American, More Than One Race)
- Self-reported Hispanic ethnicity (yes/no)

D.13.2.2. *Socioeconomic characteristics*

- Primary residential address
- Type of residence: Home, nursing home, assisted living facility, rehabilitation or skilled nursing facility
- Insurance status at baseline and annual follow-up visits (uninsured, self-insured, commercial/fee-for-service, HMO, Medicare, Medicaid, military, COBRA, other for US sites; Provincial/Public health insurance and private/personal insurance for Canadian sites)

D.13.2.3. *Past medical history*

In addition to information on exclusion criteria, we will collect data on the following comorbid conditions based on medical records review and/or patient self-report:

- Diabetes mellitus (type 1 or 2, unknown)
- Chronic heart failure
- Coronary heart disease (myocardial infarction, revascularization)
- Systemic hypertension
- Malignancy other than non-melanoma skin cancer
- Chronic lung disease (chronic obstructive lung disease, reactive airway disease)
- Chronic liver disease (cirrhosis, chronic hepatitis)
- Smoking status (never, former, current)

D.13.2.4. *Selected renal history*

- Known CKD diagnosis
- Kidney stones
- Known proteinuria
- Urinary tract obstruction

D.13.2.5. *Pre-admission medication use*

- ACE inhibitors
- Angiotensin II receptor blockers (ARBs)
- Aldosterone receptor antagonists

- Diuretics
- Other antihypertensive agents
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Insulin
- Oral anti-diabetic agents
- Lipid-lowering agents

D.13.2.6. *Medications given anytime during the index hospitalization*

The following medications will be ascertained based on receipt during any part of the index hospitalization:

- Aminoglycosides
- Amphotericin
- NSAIDs
- Vasopressors
- Diuretics

D.13.2.7. *Targeted in-hospital exposures or complications*

- Intravenous contrast given at any time during the index hospitalization for all participants and for AKI participants, whether it was given within 48 hours before the AKI event
- Sepsis based on physician-assigned diagnosis
- Acute heart failure based on physician-assigned diagnosis
- Shock of any type based on physician-assigned diagnosis
- Acute myocardial infarction based on physician-assigned diagnosis
- Respiratory failure requiring mechanical ventilation for >48 hours
- Surgical procedure (CABG, other vascular, non-vascular)

D.13.2.8. *Other inpatient data elements*

- Serum creatinine measures during hospitalization. For participants who have more than one serum creatinine measure per inpatient calendar day, the peak value per calendar day will be recorded.
- Results from any renal biopsy occurring during index hospitalization
- Acute dialysis days (treatment start and end dates) and modality (IHD, SLED, CRRT)
- ICU length of stay
- Total hospital length of stay

D.13.2.9. *Severity of illness composite measures*

The Steering Committee carefully considered the use of severity of illness scores (e.g., APACHE II or III, SOFA, SAPS) to compare AKI and non-AKI participants. Ultimately, we decided not to incorporate any of these scoring systems into ASSESS-AKI for several reasons.

First, these severities of illness scores have only been validated in critically ill ICU patients who will only be a subset of study participants in ASSESS-AKI. It is unclear how well these predictive models perform in patients who are intubated in the post-operative (e.g., post-CABG) setting or patients who are not in the ICU. In addition, it is unclear what proportion of routine post-operative CABG patients or non-ICU patients would have the laboratory data required for these severity of illness scores (e.g., bilirubin or albumin) but it is likely to be a high proportion of participants with systematically missing data.

Second, even among ICU patients, it is unclear when to compare AKI and non-AKI participants. For example, when should the scores be measured (e.g., which day of ICU admission? which day during AKI episode?) or should they be calculated daily and only the highest severity of illness score during a hospitalization be selected? Furthermore, while the first day of AKI would be clear for AKI participants, it is unclear what time point would be comparable in non-AKI participants since there is no anchoring event during the index hospitalization.

Third, these scoring systems all incorporate measures of renal function, so AKI participants will be likely to have systematically higher scores than participants without AKI. Measures of renal function could be eliminated from the severity of illness scores, but we felt that severity of illness scores without serum creatinine would then not be interpretable with regard to improving control of confounding for outcomes such as mortality. Similarly, predictive models for mortality in patients with AKI (e.g., Liano[102] and Mehta[103] models) cannot be used to measure severity of illness among non-AKI participants.

Overall, the Steering Committee concluded that we should pursue a strategy of identifying targeted potential confounding variables (outlined in *Sections D.13.2.1-D.13.2.8*) rather than attempting to collect and incorporate physiologically relevant data using one of the summary scoring systems.

D.13.3. Follow-up Data Collection Schedule and Methodology

The follow-up schedule and proposed data collection are summarized in Table 12 below for all ASSESS-AKI participants. During the three-month study visit and all subsequent phone contacts and in-person study visits, we will collect relevant exposure and outcome data. These data elements were chosen to facilitate completion of the project Specific Aims, promote long-term retention and tracking, and also to promote opportunities for future exploratory research efforts. The proposed instruments and approaches were selected to also facilitate potential collaborations with other NIDDK-sponsored prospective cohort studies of renal disease (e.g., CRIC[95]). Additional details for specific measures are provided in subsequent sections.

Table 12. Summary table of proposed data collection elements, frequency, and timing for outpatient study visits and participant contacts through the Year 4 follow-up visit.

Schedule		Year 1		Year 2		Year 3		Year 4	
Months	3	6	12	18	24	30	36	42	48
Type of Contact	Visit	Phone	Visit	Phone	Visit	Phone	Visit	Phone	Visit
Consent for long-term follow-up	●								●
Update contact info	●	●	●	●	●	●	●	●	●
Medications	●	●	●	●	●	●	●	●	●
Events	●	●	●	●	●	●	●	●	●
Collect DNA	●Adults		●Peds						
Collect specimens	●		●		●		●		●
Height and weight	●		●		●		●		●
Blood pressure	●		●		●		●		●
Questionnaires									
Demographic characteristics	●								
Lifestyle habits	●		●		●		●		●
Medical History	●		●		●		●		●
Quality of life and functional status (SF-12 in adults, PedsQL in children)	●		●		●		●		●
Cognitive function (3-MS, TRAILS B)	●		●		●TRAIL S B only		●		
Electrocardiogram (adults)	●		●		●		●		●

Schedule	Year 5		Year 6		Year 7		Year 8	
Months	54	60	66	72	78	84	90	96
Type of Contact	Phone	Visit	Phone	Visit	Phone	Visit	Phone	Visit
Consent for long-term follow-up	●							
Update contact info	●	●	●	●	●	●	●	●
Medications	●	●	●	●	●	●	●	●
Events	●	●	●	●	●	●	●	●
Collect specimens		●		●		●		●
Height and weight		●		●		●		●
Blood pressure		●		●		●		●
Questionnaires								
Lifestyle habits		●		●		●		●
Medical History		●		●		●		●

Schedule	Year 5		Year 6		Year 7		Year 8	
Months	54	60	66	72	78	84	90	96
Type of Contact	Phone	Visit	Phone	Visit	Phone	Visit	Phone	Visit
Quality of life and functional status (SF-12 in adults, PedsQL in children)		●		●		●		●
Electrocardiogram (adults)		●		●		●		●

D.13.4. Primary Outcomes

D.13.4.1. *Renal Outcomes*

Definition of kidney function and change in kidney function

Kidney function will be defined before and after an AKI episode (as well as among non-AKI participants) using eGFR from *outpatient* serum creatinine levels (mg/dL). Given the known limitations of using serum creatinine alone as a measure of kidney function,[104] except for its use in defining an episode of AKI per the criteria described in *Section D.5.2*, we propose to use the CKD-EPI[80] equation to estimate GFR among all adult ASSESS-AKI Study participants.

As noted previously, for the pediatric participants enrolled from the TRIBE-AKI, estimated GFR will be calculated using the Schwartz equation (Estimated GFR (mL/min/1.73 m^2) = 0.413 (Height, cm) / serum creatinine, mg/dL) [89] Because GFR physiologically increases from birth up until about 1 to 2 years, it is problematic to use eGFR as an outcome for comparing AKI versus non-AKI patients in groups of patients with varying ages. For example, a child may have a GFR of 50 ml per minute per 1.73m^2 at the age of 4 months old, which may be normal; however, at age 1.5 or 2 years old, this GFR would be low.

In order to account for the physiologic increase in GFR with age, we will express eGFR as percentile values according to age (similar to the way height is expressed in terms of percentiles). This will allow for meaningful comparison of AKI versus non-AKI children, regardless of age. This eGFR percentile method has been published in a manuscript by the TRIBE- AKI group [90] and used by this group to express baseline eGFR in several AKI manuscripts. [90] [91] [92] The percentiles values were derived using data from 623 children without chronic kidney disease, who had nuclear medicine GFR testing performed.

Creatinine based eGFR will be the primary method for estimating GFR. However, eGFR will also be estimated using serum cystatin C (CysC-eGFR). Though SCr is the traditional method to estimate GFR, CysC may be a more accurate marker of GFR. Several CysC-eGFR equations exist or are being developed and validated. At the time of analysis, the CysC-eGFR equation which has been best validated will be used.

The ASSESS-AKI Central Laboratory will measure standardized serum creatinine based on isotope dilution mass spectrometry (IDMS) traceable calibrated serum creatinine assays. This is a result of the National Kidney Disease Education Program which launched the Creatinine Standardization Program to

address inter-laboratory variation in creatinine assay calibration and provide more accurate estimates of GFR.[81,105] These standardized serum creatinine values can be used with the CKD-EPI[80] equation to greatly reduce bias in GFR estimation due to inter-laboratory differences in calibration. If an outside laboratory is using the Siemens/Dade Dimension or NOVA whole blood analyzer, the serum creatinine is considered to be non-IDMS calibrated.

We propose to use the CKD-EPI[80] equation with standardized serum creatinine measurements based on the best currently available evidence as of September 2010 demonstrating that it appears to perform better in the subgroup of eGFR 60-89 ml/min/1.73m^2, where the current MDRD equation tends to underestimate actual kidney function.[106,107]. We are well aware of the continued evolution in thinking about GFR estimating equations and the ongoing research in this area. Should there be a better equation developed for estimating kidney function (based on serum creatinine or other filtration marker[s]) available during the ASSESS-AKI follow-up, we can easily adopt use of the more accurate equation.

Despite its limitations, using the CKD-EPI[80] equation for assessing the level and change in kidney function over time will be highly cost-effective (compared with direct GFR testing) and will allow us to compare results with other national studies that have either been published or are ongoing which examine longitudinal changes in kidney function.

Incident CKD

Among participants without pre-existing CKD at the index hospitalization, we will examine time to development of incident CKD with significant loss of renal function defined as experiencing at least a 25% reduction in level of eGFR compared with baseline (i.e., before the index hospitalization) AND achieving CKD Stage 3 or worse[108] during follow-up.

Progression of CKD

Among participants with pre-existing CKD at the index hospitalization (defined as an eGFR <60 ml/min/1.73 m^2), we will examine time to progression of CKD, defined as experiencing at least a 50% reduction in level of eGFR compared with baseline OR progressing to CKD Stage 5.[108]

Development of End-Stage Renal Disease

Development of ESRD during follow-up will be separately defined as any of the following: (1) receipt of any outpatient dialysis after V3M; (2) death while receiving inpatient dialysis lasting ≥28 days; and/or (3) receipt of a kidney transplant.

Incident or Recurrent Episodes of AKI

We will attempt to ascertain incident and recurrent episodes of AKI. Based on available data collected during follow-up, we will use the same criteria described above in *Section D.5.2* to define incident (among non-AKI participants) or recurrent (among AKI participants) episodes of AKI. However, we recognize that some study participants may be hospitalized at non-CRC facilities where complete medical and laboratory records may not be available (and where non-IDMS serum creatinine assays may be used) and that it can be challenging to determine whether observed changes in serum creatinine reflect progression of kidney dysfunction or a new episode of AKI.

D.13.4.2. *Cardiovascular Outcomes*

To maximize future collaborations with other studies focused on kidney disease among adult populations, we have modeled our definitions after those used in the CRIC Study[95] which were derived from various NIH-sponsored longitudinal studies (Cardiovascular Health Study [CHS],[109] Atherosclerosis Risk in Communities [ARIC][110] and Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial [ALLHAT][111]).

The general approach will be to obtain self-reported and/or database information on potential outcome events and subsequently obtain information on qualifying ICD codes at each site which will facilitate review of relevant medical records to adjudicate. The following outcomes are only relevant for the subgroup of adult participants given that they are extremely rare among children.

Coronary Heart Disease: Standard definitions will be used to classify a coronary heart disease event.

- Acute coronary syndrome will be based on documented evidence of ischemic symptoms plus: transient ST-T wave changes and no elevated cardiac enzymes such as cardiac troponin (i.e., unstable angina); elevated cardiac enzymes without ST-elevation on ECG (i.e., non-ST-elevation myocardial infarction); or elevated cardiac enzymes and ST-elevation or Q waves on ECG (i.e., ST-elevation myocardial infarction).[112,113] This will be based on ICD-9 codes of 410.0-.9, 411.0-.1, and 411.81-.89 and corresponding ICD-10 codes.
- Sudden cardiac death will be obtained by mortality files and subject proxy contacts. It will be defined as either an unwitnessed death without another obvious cause or death occurring within one hour of the onset of ischemic symptoms per a proxy.[114]
- Heart failure will be based on hospitalizations for a clinical heart failure syndrome using primary discharge ICD-9 codes of 398.91, 402.01-.11, 402.91., and 428.0-.9. or corresponding ICD-10 codes and confirmed based on Framingham Heart Study clinical criteria ascertained from medical records.[115] We will not require evidence of systolic dysfunction (e.g., left ventricular ejection fraction <40%) or diastolic dysfunction on echocardiography.[116]
- Coronary artery revascularization will include either percutaneous coronary intervention with or without intracoronary stenting or coronary artery bypass surgery of one or more coronary blood vessels (ICD-9 codes 36.01-.02, 36.05-.06, 36.09, 36.10-.17, and 36.19 and corresponding ICD-10 codes).
- Silent myocardial infarction will be defined as new, pathologic Q waves on serial electrocardiograms (ECG)[117] among the subgroup of enrolled adult participants with the event date assigned as the mid-point between the relevant annual visits.

Cardiac Arrhythmias and Electrocardiographic Abnormalities will be based on serial electrocardiograms using WHO[118] and the Minnesota Code definitions,[119] which have been used in epidemiological studies and have direct clinical applicability. These include development of atrial fibrillation, atrial flutter, left and right bundle branch block, atrioventricular conduction defects, and left ventricular hypertrophy among others.

Cerebrovascular Disease Outcomes: The pertinent cerebrovascular disease outcomes include ischemic stroke and intracranial hemorrhage, and carotid endarterectomy.

- Ischemic stroke will be defined as acute development of a neurological deficit fitting a vascular distribution, lasting ≥24 hours, and no other evident etiology such as intracranial hemorrhage, vasculitis, tumor, or trauma. This definition has been validated in other epidemiological studies.[120,121] (ICD-9 codes 433.00-.01, .10-.11, .20-.21, .30-.31; 434.00-.01, .10-.11, .90-.91; and 436.0 and corresponding ICD-10 codes). Supporting brain imaging (e.g., CT or MRI) will be sought but will not be required for diagnosis.
- Intracranial hemorrhage will require validation by brain imaging or pathologic evidence, and should have a documented history consistent with a stroke syndrome, diminished consciousness, or headache (ICD-9 codes 430, 431, 432.0-.9, 852.0, 852.2, 852.4, 853.0 and corresponding ICD-10 codes).[122]
- Carotid endarterectomy will include both surgical endarterectomy and balloon angioplasty with or without carotid stent placement (ICD-9 codes 38.12, 38.32, 38.42 and corresponding ICD-10 codes).

Peripheral Arterial Disease Outcomes: Pertinent outcomes include intermittent lower extremity claudication, and lower extremity arterial revascularization or amputation for refractory ischemia.

- Lower extremity revascularization will include both percutaneous peripheral artery angioplasty and surgical arterial bypass procedures (ICD-9 codes 38.18, 38.38, 38.48, 39.50 and corresponding ICD-10 codes), and lower extremity amputation will include procedures performed for refractory ischemia (ICD-9 codes 84.10-.17 and corresponding ICD-10 codes).
- Thoracic or abdominal aortic aneurysm dissection, rupture or repair (using percutaneous or surgical procedures) based on corresponding ICD-9 diagnosis (441.0, 441.3) and procedure (39.71, 38.44, 39.25, 39.52, 38.34, 38.64, 38.40, and 38.60) codes, and corresponding ICD-10 codes, and as needed, relevant ICD-9 CPT and ICD-10 CCI procedures codes.

D.13.4.3. *Mortality*

As described in *Section D.11*, deaths will be identified primarily through surveys of subjects or their proxy contacts and review of medical records or death certificates, if available. Secondarily, we will seek to obtain information on social security number from participants to conduct probability matches with Social Security Administration vital status files[123] and National Death Index[100] among the subset set of participants who are lost to follow-up. All-cause mortality will be the preferred outcome given known significant errors in assigning etiology.[124]

D.13.5. Secondary Outcomes

D.13.5.1. *Renal*

Below are the proposed secondary renal-related outcomes:

- ≥ 25% relative change of eGFR from baseline or dialysis/transplant
- Composite index of ESRD or death
- Progression to a more advanced stage of CKD

- Slope change defined as a percentage change in rate in slope of decline of eGFR during follow-up
- Development of or change in magnitude of proteinuria

D.13.5.2. *Functional Status*

Functional status will be assessed using the SF-12v2™ Health Survey in adult participants and PedsQL in children. These measures are widely used in both renal and non-renal populations.[125]

D.13.5.3. *Cognitive function*

Cognitive function assessment will be measured by the Modified Mini-Mental Status Examination (3MS)[126] which has been used widely for assessment of global cognitive function. The 3MS will be conducted during the 3-, 12-, and 36-month, adult, in-person visits, although it can also be conducted by telephone in participants who are not able to complete an in-person study visit. We also note that cognitive function will not be performed in enrolled pediatric participants as the 3MS is not possible to administer reliably in these participants.

TRAILS B is to be administered at the 3-, 12-, 24-, and 36-month, adult, in-person visits and prior to the Modified Mini-Mental Status Examination (MMMSE) if applicable. It offers an assessment of cognitive function with the sensitivity for detecting cognitive dysfunction and it is brief. TRAILS B is not administered to the pediatric participants. TRAILS A is not administered.

D.13.5.4. *Blood pressure and hypertension*

Blood pressure changes and development of hypertension based on automated blood pressure measurement at study visits by trained research personnel; self-report of a physician diagnosis of hypertension; and/or evidence of a new prescription of an anti-hypertensive agent for the indication of hypertension.

D.13.5.5. *Hospitalizations for any cause*

All hospitalizations will be ascertained, regardless of the reason for admission, as this is one of the biggest drivers of healthcare costs in the U.S.

D.13.6. Biomarker Selection

D.13.6.1. *Core clinical measures*

Adults and Children:
Collection of inpatient serum creatinine values will be required for all hospitalizations prior to onset of ESRD.

Adults: Serum creatinine, blood urea nitrogen, electrolytes, glucose, LDL cholesterol, HDL cholesterol, triglycerides, serum cystatin C, urine creatinine, urine protein, urine albumin will be done by the Central Lab. A complete blood count (WBC, hemoglobin, platelet count) at every visit and serum Creatinine at the

three-month visit will be done by the local lab. The serum Creatinine done by the local lab was stopped on May 30, 2012.

Children: Serum creatinine, serum cystatin C, urine creatinine, urine protein, urine albumin will be done by the Central Lab. There will be no CBC or serum creatinine collected for the pediatric participants and sent to the local lab in order to have more sample available for aliquoting.

Urinalysis: Standard urine analysis performed by the coordinator using the Bayer Clinitek will be performed ONLY on an in-hospital urine sample from non-AKI participants and participants with AKI collected 96 hours after the AKI occurrence. This is performed for adult participants and suggested for pediatric participants.

D.13.6.2. *Novel Biomarkers*

As part of the preparation of the protocol, the Steering Committee carefully reviewed available studies of potential novel biomarkers in the setting of AKI. Below is a table showing a preliminary list of novel biomarkers that will be considered for testing within ASSESS-AKI (Table 13A). This table summarizes data on how the biomarker has been evaluated to date, discovery method, available assay platforms, minimum sample requirements, if known, and processing and storage requirements or limitations. Refer to Appendix I., *ASSESS AKI Novel Biomarker Measurements – Adults,* and II., *ASSESS AKI Novel Biomarker Measurements – Pediatrics,* for the current list of analyzed biomarkers for the ASSESS AKI Main Study (adult and pediatric) and ancillary studies.

Tier 1 Biomarkers: Markers with the strongest current clinical evidence base as markers of early AKI. In these cases, we will propose to measure these biomarkers in all study participants using a derivation set/validation set approach. Given the current data supporting the use of these markers in clinical studies for the detection of AKI, it will be important to know whether these markers predict short or long term outcomes. Results will be informative whether or not there is an association of the biomarker with outcomes.

Tier 2 Biomarkers: Markers where the evidence supporting their use as biomarkers of AKI is more limited. In these cases, to efficiently test as many of these markers as possible (both from a sample and cost perspective), we will start with a nested case-control approach. If the nested case-control study suggests that these markers are promising markers of disease, we will move to a derivation set/validation set approach as for the Tier 1 biomarkers. This list of biomarkers is long, since we have included all markers where there are clinical studies suggesting that these markers have clinical utility for detection or prognosis in the setting of AKI or where there is sufficiently compelling animal data that human diagnostic tests have been developed (e.g. Human KidneyMap,™ Rules Based Medicine) and are in use. We will prioritize this list of biomarkers based on currently available evidence and future studies as these become available.

Tier 3 Biomarkers: Markers where there are human studies suggesting that these markers may have predictive value for AKI and where currently available assays for human samples are not feasible for large-scale studies. These markers will be reprioritized if new assays become available. This list does not include markers where no human assay is currently available (e.g., Cyr61).

Table 13A. Novel biomarkers for AKI, prior evaluation for selected outcomes, and testing and storage requirements.

Biomarker	TIER	Goal(s) of Marker	Discovery Method*	Bioassay Platform	Volume required*	Processing/ storage requirements	Clinical References
URINE							
Urinary IL-18	**1**	Detection, prognosis (death)	Caspase 1 deficient mouse model	ELISA/ architect	50-100 microliters		Parikh 2004, Parikh 2006
Urinary NGAL	**1**	Detection, prognosis (RRT, death)	Microarray	ELISA/ architect	50-100 microliters	Unstable at minus 20°C for prolonged periods	Mishra 2005, Nicolas 2008
Urinary KIM-1	**1**	Detection, prognosis (death)	Representational difference analysis	ELISA or Luminex (Bonventre)	200 microliters		Han 2002, 2008, Liangos 2007
Urinary cystatin C	**1**	Prognosis (RRT)	Physiology	Nephelometry (Siemens)	80 microliters		Herget CC 2004
Urinary L-FABP	**1**	Detection	Analogy to CKD	ELISA (CMIC)	100 microliters		Nakamura 2006, Portilla 2008
Urinary NAG	**1**	Detection, prognosis (RRT, death)	Physiology	Enzymatic assay (Roche)	10 microliters		Liangos 2007, Han 2008
Urinary a1-microglobulin	**2**	Detection	Physiology	Nephelometry (Siemens)	20 microliters		Herget CC 2004
Urinary MMP-9	**2**	Detection	Protein expression analysis	ELISA (R&D Systems)	200 microliters		Han 2008
Urinary NHE-3	**3**	Detection	Immunoblot	Western blot	TBD	Requires differential centrifugation	Du Cheyron 2003
Urinary fetuin A	**3**	Detection	2-DIGE of urinary exosomes	Western blot	TBD	Requires differential centrifugation	Zhou 2006
Urinary netrin	**2**	Detection	Protein expression analysis	Western blot	1 mL		Reeves 2008
Urinary a-GST	**2**	Detection, prognosis (RRT)	Physiology	ELISA (Biotrin)	80 microliters	Requires special storage buffer	Westhuyzen 2003, Herget CC 2004, Eijkenboom 2005
Urinary p-GST	**2**	Detection	Physiology	ELISA (Biotrin)	80 microliters	Requires special storage buffer	Westhuyzen 2003, Eijkenboom 2005
Urinary GGT	**2**	Detection, prognosis (RRT)	Physiology	Enzymatic assay (Roche)	2 mL		Westhuzyen 2003, Herget CC 2004

Table 13A. Novel biomarkers for AKI, prior evaluation for selected outcomes, and testing and storage requirements. (cont'd)

Urinary alkaline phosphatase	**2**	Detection	Physiology	Clinical lab analyte	TBD		Westhuyzen 2003
Urinary retinol binding protein	**2**	Prognosis (RRT)	Physiology	Nephelometry (Siemens)	50 microliters		Herget CC 2004
Urinary clusterin	**2**	Detection	PSTC*	Luminex (RBM)	30 microliters		
Urinary b2-microglobulin	**2**	Detection	PSTC*	Luminex (RBM)	30 microliters		
Urinary trefoil factor 3	**2**	Detection	PSTC*	Luminex (RBM)	30 microliters		Biomarkers Partner Presentation, 4/23/09
Urinary calbindin	**2**	Detection	Human KidneyMapTM	Luminex (RBM)	30 microliters		Biomarkers Partner Presentation, 4/23/09
Urinary osteopontin	**2**	Detection	Animal models	Luminex (RBM)	30 microliters		Biomarkers Partner Presentation, 4/23/09
Urinary VEGF	**2**	Detection	Animal models	Luminex (RBM)	30 microliters		Biomarkers Partner Presentation, 4/23/09
Urinary TIMP-1	**2**	Detection	Animal models	Luminex (RBM)	30 microliters		Biomarkers Partner Presentation, 4/23/09
Urinary CTGF	**2**	Detection	Human KidneyMap	Luminex (RBM)	30 microliters		Biomarkers Partner Presentation, 4/23/09
Urinary Tamm Horsfall protein	**2**	Detection	Human KidneyMap	Luminex (RBM)	30 microliters		Biomarkers Partner Presentation, 4/23/09
SERUM/PLASMA							
Serum cystatin C	**1**	Detection, prognosis (RRT)	Analogy to CKD	Nephelometry (Siemens)	30 microliters		Herget KI 2004, Mazul-Sunko 2004, Ahlstrom 2004
Serum pro-ANP	**2**	Detection	Analogy to CKD	ELISA (Biomedica Gruppe)	20 microliters		Mazul-Sunko 2004
Serum NGAL	**1**	Detection, prognosis (RRT, death)	Microarray	ELISA/ POCT (TRIBE-Biosite)	50 microlitre		Mishra 2005

Table 13A. Novel biomarkers for AKI, prior evaluation for selected outcomes, and testing and storage requirements. (cont'd)

Plasma IL-6	**1**	Detection, prognosis (death)	Physiology	ELISA (R&D) or Luminex	200 microliters		Iglesias 2003, Chawla 2007, Liu 2007, Simmons 2004, Ahlstrom 2004
Plasma IL-8	**2**	Prognosis (death)	Physiology	ELISA (R&D) or Luminex	100 microliters		Simmons 2004, Ahlstrom 2004
Plasma IL-10	**2**	Prognosis (death)	Physiology	ELISA (R&D) or Luminex	400 microliters		Simmons 2004, Ahlstrom 2004
Plasma sTNFR-I	**2**	Detection	Physiology	ELISA (R&D)	50 microliters		Iglesias 2003, Liu 2007
Plasma sTNFR-II	**2**	Detection	Physiology	ELISA R&D)	50 microliters		Iglesias 2003, Liu 2007
Plasma PAI-1	**2**	Detection	Physiology	ELISA (R&D)	100 microliters		Liu 2007
Neutrophil CD-11b	**3**	Detection	Physiology	Flow cytometry	TBD	Requires cell isolation-fresh blood	Rinder 2003

* For ELISA and enzymatic assays, reflects volume for duplicate assay; # Requires sufficient urine for differential centrifugation; published studies have used approximately 10-15 mL of urine; $ Requires sufficient blood for buffy coat isolation, usually 3-5 mL

Table to be reviewed annually and may add or delete based on new knowledge evolves.

Table 14. Important laboratory characteristics on the primary biomarkers of AKI.

Biomarker	Platform	Volume required	Freeze/thaw stability	Storage stability	Processing	Protease Inhibitors
Plasma/Urinary cystatin C	Siemens nephelometer	100 microliters	At least 3 cycles	Up to 1 year at -80°C	Stable at 4°C x 1 week*	Not needed
Urinary IL-18	ELISA/Architect	100 microliters	At least 3 cycles	Years at -80°C	Stable at 4°C x 24 hours	Not needed
Urinary Kim-1	Luminex	30 microliters	At least 5 cycles	Up to 2 years at -80°C	Ideally within 1 hour, but stable for several hours at 4°C	Not needed
Urinary L-FABP (CMIC)	ELISA (high throughput platform pending)	100 microliters	At least 6 cycles	Up to 6 years at -80°C	Stable at room temperature for up to 48 h	Not needed
Urinary N-acetylglucosaminadase	Luminex (alternate assay: enzymatic)	30 microliters	At least 5 cycles	Up to 2 years at -80°C	Ideally within 1 hour, but stable for several hours at 4°C	Not needed

Table 14. Important laboratory characteristics on the primary biomarkers of AKI. (cont'd)

Plasma/Urinary NGAL	Abbott Architect	10 microliters	At least 3 cycles	Up to 1 year at -80°C	Collect and store at 4 degrees, process within 24 hours	Not needed
Plasma IL-6	Luminex (alternate assay: ELISA)	30 microliters	At least 4 cycles	Several years at -80°C**	Stable for several days at 4°C **	Not needed

* Herget-Rosenthal, Ann Clin Biochem 2004; 41: 111–118
** Kennis et al, Cytokine 2002; 19: 228-235

D.13.6.3. *Selection of biomarker partners and evaluation of new putative markers for AKI*

The Steering Committee will seek academic and industry stakeholders involved in biomarker discovery and development to identify biomarker partners that will provide input to the Steering Committee in the final selection of biomarkers to test and associated requirements for sample collection, processing, storage and testing.

After review of the literature and surveying available commercial entities involved in biomarker development or testing, ten potential biomarker partners will be invited to attend a meeting on April 23, 2009 in Dulles, VA. At that meeting, each party will present information on: putative biomarkers they are involved in testing (serum, plasma, and/or urine), associated pre-clinical data, published or unpublished clinical data in AKI and/or CKD patients, volume of sample required and any special sample handling and storage requirements, details on their measurement platform and analytic variability, stability of biomarkers (i.e., freeze and thaw impact, storage conditions, temperature, etc.), potential for financially supporting testing of samples collected in the ASSESS-AKI cohort, and any plans for submission to the FDA.

Following the meeting, a summary document will be created to review key details by the Biomarker Committee and initial recommendations made to the Steering Committee about revising the proposed core biomarker set and biomarker partnerships to pursue. The Steering Committee will modify the ASSESS-AKI sample collection and processing protocol, if necessary, based on the input from the meeting.

For any biomarker partnerships that are initiated, the following principles will be applied:

- Only de-identified samples will be transferred for testing
- There will be no individual data sharing by ASSESS-AKI and only summary results shared
- The contribution of the biomarker partner will be acknowledged in any ASSESS-AKI manuscript
- Participation in ASSESS-AKI manuscripts is not guaranteed and will be governed by the Steering Committee and be consistent with current authorship requirements

D.13.6.4. *DNA*

DNA collection for adult and pediatric participants is described in Figures 12 and 13 in *Sections D13.7.1. and D13.7.2.* The ASSESS-AKI DCC will coordinate the tracking of samples throughout the process from collection to final storage of aliquots of extracted DNA that will reside at the NIDDK Biorepository.

- Adults. The ASSESS-AKI Consortium will partner with the ASSESS AKI Central Lab (University of Minnesota) for the extraction of DNA from the adult participants and the NIDDK Biorepository (Fisher) for the storage and retrieval of DNA samples obtained from adult cohort members for future genetic studies related to AKI and associated clinical outcomes. Frozen packed cells will be collected among adult participants at the three-month study visit.

- Pediatrics. The ASSESS AKI Consortium will partner with the NIDDK Biorepository (Rutgers) for the creation of immortalized cell lines of the DNA from the pediatric participants and with the ASSESS AKI Central Lab for the extraction of DNA from frozen packed cells for those pediatric participants for whom a cell line could not be created. Frozen packed cells will be collected during the inpatient visit and stored at the site as a backup until the completion of the 12-month visit. Whole blood will be collected to create an immortalized cell line at the twelve-month visit. If unable to collect the whole blood, future attempts will be made at the yearly in-person visits. If unsuccessful, the frozen packed cells collected during the inpatient phase will be sent to the Central Lab for DNA extraction. If the frozen packed cells are not needed for ASSESS AKI, they will be stored as TRIBE AKI samples.

D.13.7. Volume, Tube and Specific Requirements for Biomarker Sample Collection

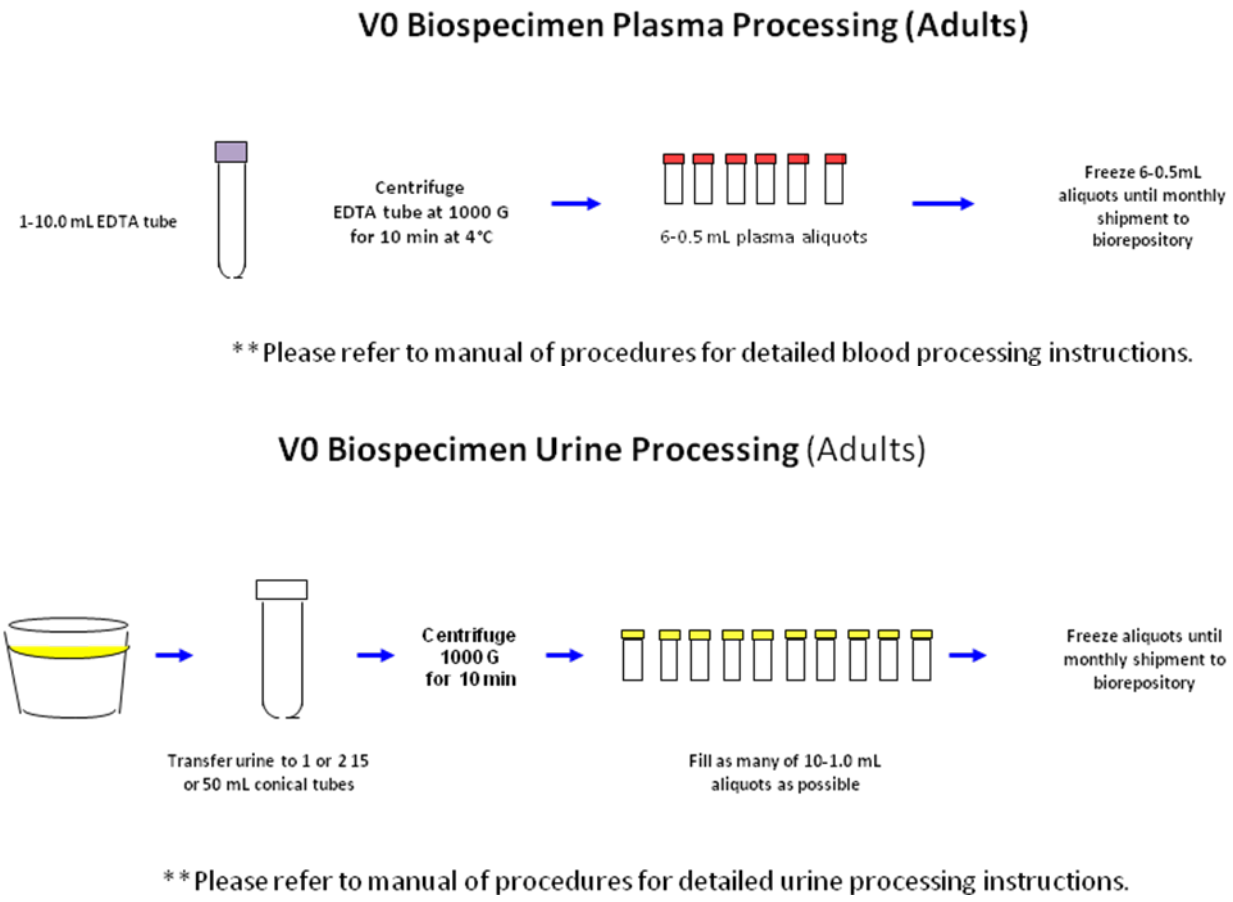
Visit	Adult					
	Minimum Urine	Goal Urine	Collection Window Urine	Minimum Blood	Goal Blood	Collection Window Blood
0	3 (1mL) aliquots	10 (1mL) aliquots	n/a	3 (0.5mL) EDTA plasma aliquots	6 (0.5mL) EDTA plasma aliquots	n/a
3M	20mL	10 (1mL) aliquots	48-hr	10mL whole blood	Serum 6 (1mL) aliquots	48-hr
		3 (10mL) aliquots			EDTA 5 (1mL) aliquots	
		PI 1 (10mL) aliquots			Citrate 2 (1mL) aliquots	
12M	0	10 (1mL) aliquots	48-hr	0	Serum 6 (1mL) aliquots	48-hr
		3 (10mL) aliquots			EDTA 5 (1mL) aliquots	
					Citrate 2 (1mL) aliquots	
24M/ 36M/ 48M	0	10 (1mL) aliquots	48-hr	0	Serum 6 (1mL) aliquots	48-hr
		3 (10mL) aliquots			EDTA 5 (1mL) aliquots	
					Citrate 2 (1mL) aliquots	
60M/ 72M/ 84M/ 96M	0	10 (1mL) aliquots	48-hr	0	Serum 6 (1mL) aliquots	48-hr
		3 (10mL) aliquots			EDTA 5 (1mL) aliquots	
					Citrate 2 (1mL) aliquots	

Vs	Pediatrics						
	Minimum Urine		Goal Urine	Collection Window Urine	Minimum EDTA Plasma	Goal EDTA Plasma	Collection Window Blood
	Diaper	Non-Diaper					
0	0	0	10 (1mL) aliquots		0	4 (0.5mL) aliquots	n/a
3M	1.6mL	5mL	10 (1mL) aliquots	48-hr	0	1 (0.5mL) aliquots	48-hr
			1 (10mL) aliquots			4 (0.25mL) aliquots	
12M	1.6mL	5mL	10 (1mL) aliquots	48-hr	0.175mL	1 (0.5mL) aliquots	48-hr
			1 (10mL) aliquots			4 (0.25mL) aliquots	
24M/ 36M/ 48M	0	0	10 (1mL) aliquots	48-hr	0	1 (0.5mL) aliquots	48-hr
			1 (10mL) aliquots			4 (0.25mL) aliquots	
60M/ 72M/ 84M/ 96M	0	0	10 (1mL) aliquots	48-hr	0	1 (0.5mL) aliquots	48-hr
			1 (10mL) aliquots			4 (0.25mL) aliquots	

Figure 11. Inpatient and Outpatient Biospecimen Collection Plan: Minima and Goals.

D.13.7.1. *Inpatient biospecimen collection plan*

The inpatient biospecimen collection and storage strategy for blood and urine during the inpatient phase is outlined in Figure 12.



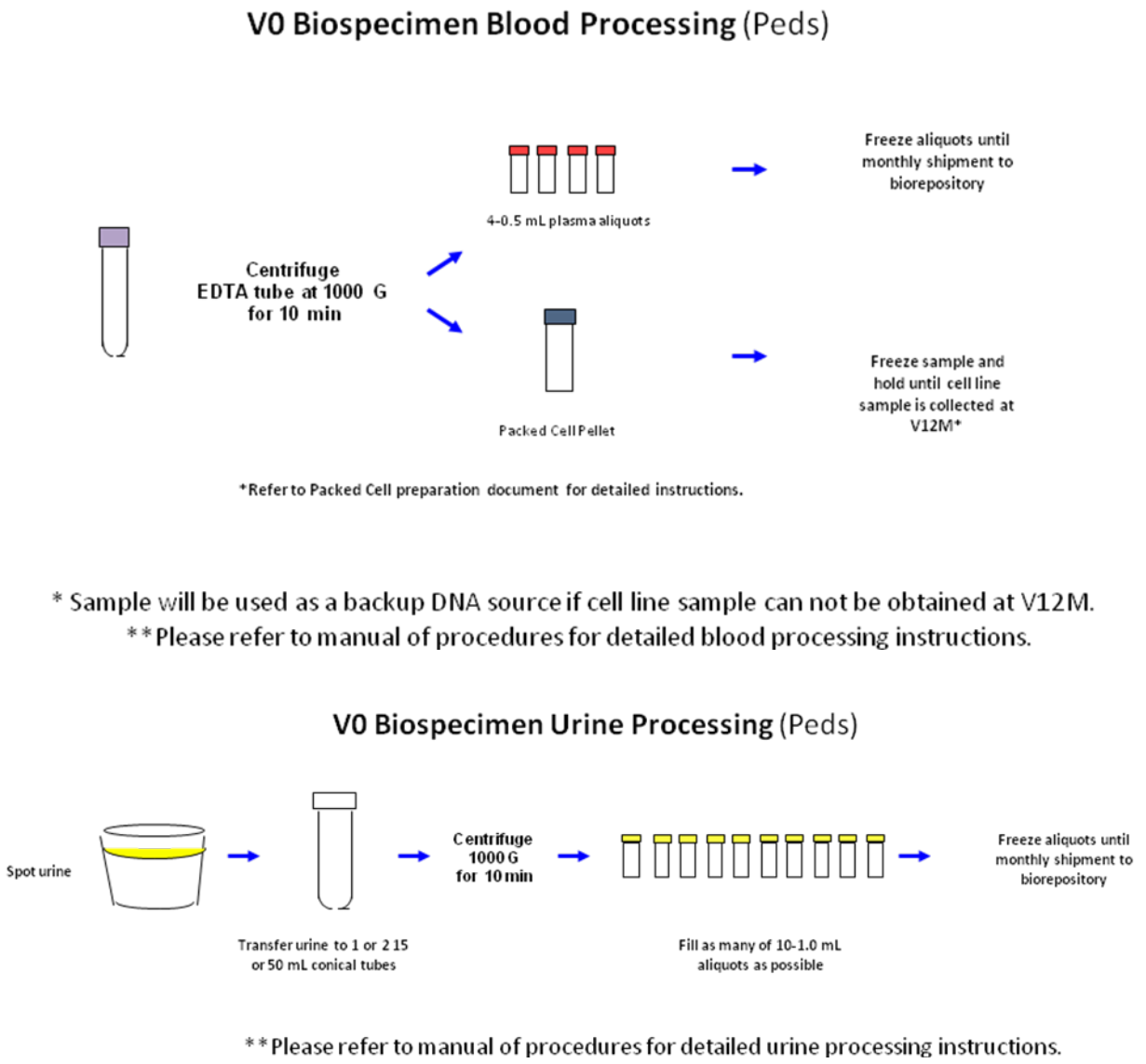


Figure 12. Sample Flow sheets of Inpatient biospecimen collection at CRC and subsequent coordination of sample processing, storage and testing.

Across all CRC's, at least one sample of blood and urine will be obtained (1) for AKI participants up to 96 hours after identification of the AKI episode and (2) for non-AKI participants any time prior to hospital discharge. Within each CRC, below are specific details about the planned available minimum volumes from inpatient samples:

- *TRIBE-AKI*. The parent cohort biospecimen sampling plan is detailed in *Section D.2.1.* At least one 2 mL sample of sera or plasma and 10 mL of urine will be available for accomplishing the proposed Aims in ASSESS-AKI.

- For the pediatric participant, there is no minimum plasma volume. However, if the child weighs less than 15 kg, an attempt to collect 1 to 3 cc should be made (not to exceed 3 cc); if the child weighs more than 15kg, an attempt to collect 5 cc of blood should be made.

- *VALID*. The parent cohort biospecimen sampling plan is detailed in *Section D.2.2*. At least one 2 mL sample of sera or plasma and 10 mL of urine will be available for accomplishing the proposed Aims in ASSESS-AKI.

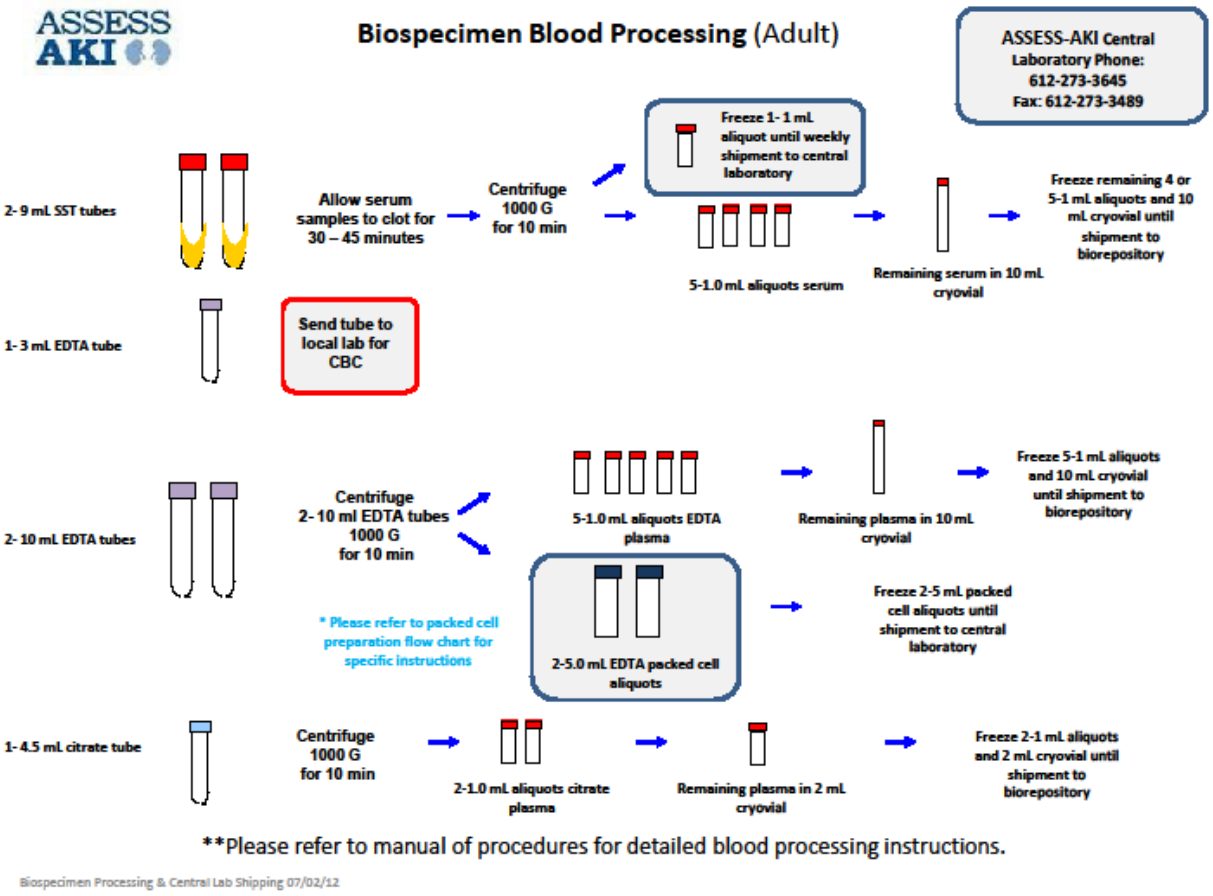
- *Kaiser Permanente of Northern California*. At least 5 mL of sera or plasma and 20 mL of urine will be obtained for accomplishing the proposed Aims in ASSESS-AKI.

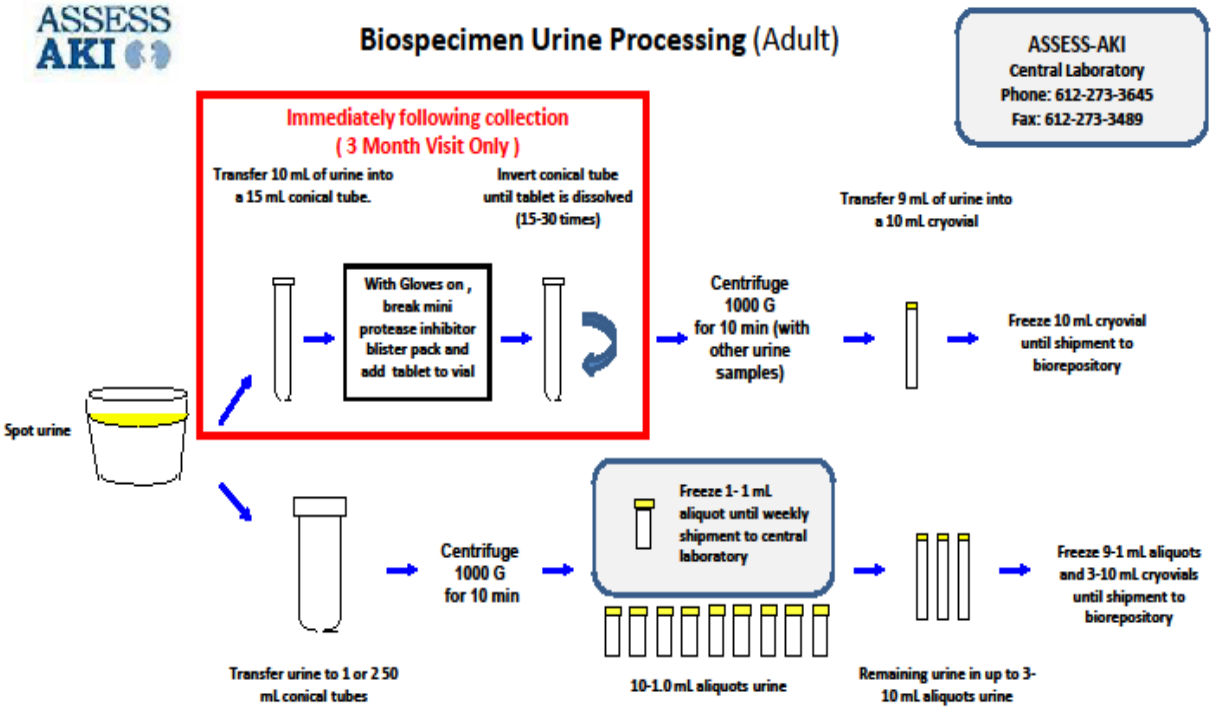
- University of Washington. At least 5 mL of sera or plasma and 10 mL of urine will be obtained for accomplishing the proposed Aims in ASSESS-AKI.

All inpatient biospecimen samples will be transferred to the NIDDK Biorepository (Fisher) for coordination of future biomarker testing and storage.

D.13.7.2. *Follow-up biospecimen collection and storage plan*

The follow-up outpatient biospecimen collection and storage strategy for blood and urine at the three-month and subsequent study visits is outlined below in Figure 13:


ASSESS AKI
Biospecimen Blood Processing (Adult)
ASSESS-AKI Central Laboratory Phone: 612-273-3645 Fax: 612-273-3489
2- 9 mL SST tubes
Allow serum samples to clot for 30 – 45 minutes
Centrifuge 1000 G for 10 min
Freeze 1- 1 mL aliquot until weekly shipment to central laboratory
5-1.0 mL aliquots serum
Remaining serum in 10 mL cryovial
Freeze remaining 4 or 5-1 mL aliquots and 10 mL cryovial until shipment to biorepository
1- 3 mL EDTA tube
Send tube to local lab for CBC
2- 10 mL EDTA tubes
Centrifuge 2- 10 ml EDTA tubes 1000 G for 10 min
5-1.0 mL aliquots EDTA plasma
Remaining plasma in 10 mL cryovial
Freeze 5-1 mL aliquots and 10 mL cryovial until shipment to biorepository
* Please refer to packed cell preparation flow chart for specific instructions
2-5.0 mL EDTA packed cell aliquots
Freeze 2-5 mL packed cell aliquots until shipment to central laboratory
1- 4.5 mL citrate tube
Centrifuge 1000 G for 10 min
2-1.0 mL aliquots citrate plasma
Remaining plasma in 2 mL cryovial
Freeze 2-1 mL aliquots and 2 mL cryovial until shipment to biorepository
**Please refer to manual of procedures for detailed blood processing instructions.
Biospecimen Processing & Central Lab Shipping 07/02/12



**Please refer to manual of procedures for detailed urine processing instructions.

Biospecimen Processing & Central Lab Shipping 03/11/10 V2.2

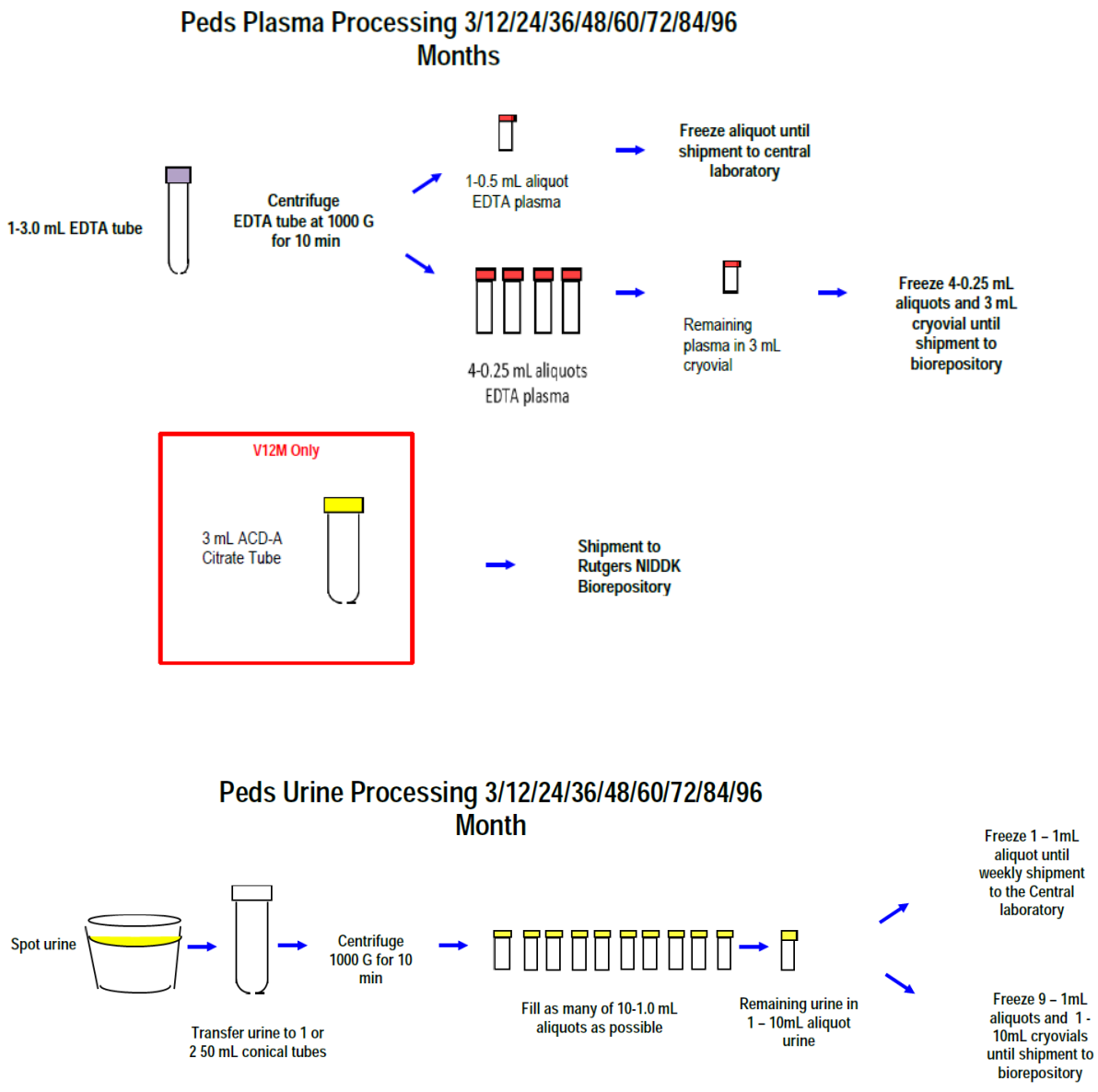


Figure 13. Sample Flow sheets of Inpatient and Outpatient biospecimen collection at CRC and subsequent coordination of sample processing, storage and testing.

Biospecimen volume collection plan

Adult Participants

Three-month visit. A total of 50 mL of blood (DNA, sera, and plasma) and 50 mL of randomly collected urine (10 mL with protease inhibitors) will be collected and processed as shown in 13 above. The samples will be stored locally at each CRC at -80°C prior to shipping to the NIDDK Repository and the Central Laboratory at the University of Minnesota.

Subsequent visits. At each subsequent study visit, 50 mL of blood and 50 mL of randomly collected urine will be collected in a sterile plastic container with no protease inhibitor and processed as shown in Figure 13 above. The samples will be stored locally at each CRC at -80°C prior to shipping to the NIDDK Repository and the Central Laboratory at the University of Minnesota.

There is a 48-hour collection window for blood and urine samples following the study visit. If the minimum is not collected within the 48-hour window, the visit may be repeated within the visit window. The proposed specimen types and volumes will facilitate measurement of currently planned biomarkers and allow adequate sample for future ancillary studies. The proposed total volumes of blood and urine are consistent with other longitudinal studies of renal disease (e.g., CRIC).

Pediatric Participants.

For pediatric participants enrolled through the TRIBE-AKI Study, we will obtain a minimum of 0.175mL of EDTA plasma, a minimum of 1.6mL of urine from diaper wearers and 5 mL of urine from non-diaper wearers, and DNA using the following approach. There is a 48-hour collection window for both blood and urine samples following the study visit. If the minimum is not collected within the 48-hour window, the visit may be repeated within the visit window.

Blood collection: Although 2.5 mL of blood is optimal for testing, 0.175mL of EDTA plasma is the mandatory minimum at V12M and will be attempted to be collected at each follow-up visit. If study visits occur during routine hospital visits and if the subject's physician requests blood from the patient for other reasons, we will obtain blood at the same time as these routine blood tests are performed through the Test Referral Center, to avoid unnecessary venipunctures. If study visits occur independent of routine clinic visits, then a research nurse, principal investigator, or GCRC staff member will obtain the blood specimen via either a venous or capillary blood draw.

Urine: Participant will void in a non-sterile cup. We will attempt to obtain up to 20 mL of urine from pediatric participants, but as little as 1.6mL of urine for diaper wearers and 5 mL of urine for non-diaper wearers is mandatory at V3M and V12M. In infants and toddlers unable to void into a specimen container, cotton balls will be placed in the diaper to collect urine.

DNA: Frozen packed cells will be obtained at the inpatient visit and stored at the site as a backup if the cell line cannot be created. Whole blood will be extracted at the twelve-month visit to obtain a sample for immortalized cell line and future testing. Future attempts will be made at the yearly visits to obtain the sample for the immortalized cell line.

Quality Control and Quality Assurance

Quality control and quality assurance methods for biospecimen collection, processing and testing will be implemented with oversight by the ASSESS-AKI Quality Control Committee in coordination with the DCC, Central Laboratory (University of Minnesota), and NIDDK Biorepository (see *Section G.8*).

E. STATISTICAL APPROACH AND POWER

E.1. Research Hypotheses

The planned statistical analyses address the six research hypotheses for the ASSESS-AKI study that are presented in Section A.4.

Hypothesis 1a. An episode of AKI independently increases the risk of incident chronic kidney disease in persons without pre-existing chronic kidney disease.

Hypothesis 1b. An episode of AKI independently increases the risk of faster progression of chronic kidney disease and development of ESRD in persons with pre-existing chronic kidney disease.

Hypothesis 2. AKI increases the short- and long-term risks of death from any cause, cardiovascular events, and other adverse outcomes (e.g., poorer cognitive function, quality of life, or functional status) in persons with and without pre-existing chronic kidney disease, even after adjustment for potential confounders.

Hypothesis 3. Novel serum and/or urine biomarkers can improve the clinical prediction after an episode of AKI using a serum creatinine-based definition.

Hypothesis 4. Greater severity of an AKI episode, presumed acute tubular necrosis etiology, and the presence and severity of pre-existing chronic kidney disease raise the risk of adverse outcomes after an episode of AKI.

Hypothesis 5. Persons who have incomplete recovery of kidney function within three months after an episode of AKI have a higher risk of adverse clinical outcomes that is mediated primarily through incident and progressive chronic kidney disease.

Hypothesis 6. A clinically useful and easily implementable risk score can be developed that integrates information on individual characteristics and/or serum/urine biomarkers to provide robust prognostic information for individuals who experience an episode of AKI.

E.2. Statistical Analyses for Hypothesis 1, Hypothesis 2, Hypothesis 4, and Hypothesis 5

The statistical analyses to investigate Hypothesis 1, Hypothesis 2, Hypothesis 4, and Hypothesis 5 are based on comparing AKI participants and non-AKI participants, or selected subgroups, with respect to time-to-event outcomes. Important events include death, CKD, myocardial infarction, congestive heart failure, etc. (see *Sections D.13.4* and *D.13.5*).

The exact dates of certain events, such as death, myocardial infarction, heart failure, etc. can be confirmed via medical charts. Therefore, the statistical analyses in these situations will invoke continuous time-to-event models that account for right-censored data.

Exact dates for the occurrence of other events, such as the onset of chronic kidney disease, may not be

confirmed in every circumstance and may only be known to occur within a specific time interval of 3-12 months, 12-24 months, 24-36 months, 36-48 months, 48-60 months, 60-72 months, 72-84 months, and 84-90 months. The endpoints of the first six time intervals correspond to the in-person study visits. Therefore, the statistical analyses in these situations also will invoke discrete time-to-event models that account for right-censored and interval-censored data.[127-128]

We will calculate unadjusted rates of each outcome (per 100 person-years) with associated 95% confidence limits for AKI and non-AKI participants, and cumulative incidence curves compared using a log-rank test. For each outcome, after confirming no violation of the proportional hazards assumption by examining log-log-survival curves, we will perform nested Fine-Gray subdistribution hazard analyses[129] accounting for individual matching and competing risk of death, with additional incremental adjustment for variables not included in the matching criteria that have been previously reported or hypothesized to be risk factors for kidney and cardiovascular events, or differing between AKI and non-AKI participants at the baseline study visit.

For cardiovascular and death outcomes, the final model will adjust for three-month post-discharge measures of kidney function and proteinuria based on *a priori* hypotheses that levels of residual kidney function and damage may explain, at least in part, any observed excess risks for these clinical outcomes after an episode of AKI. We will evaluate the performance of the statistical models overall and stratified by pre-existing CKD status, as appropriate. Because outcomes are time-to-event with right-censoring due to death, study withdrawal or end of study follow-up, we will not impose any procedure to account for potential missingness in the outcomes.

We will separately examine the association of severity of the index AKI episode with outcomes of interest by modeling KDIGO stage of AKI (1, 2 or 3) as a linear term. Because our matching algorithm does not result in an exact one-to-one match on all criteria in the AKI and non-AKI participants, we also will conduct sensitivity analyses among the subset of patients placed within the strata who were exactly matched on all individual matching criteria within each stratum.

We will modify the statistical models described above for a separate analysis of the Yale children because the AKI and non-AKI children did not undergo one-to-one matching.

Subgroup analyses, in addition to those specified in the research hypotheses, will be conducted for pre-existing conditions (such as diabetes or cardiovascular disease), severity of AKI injury, etc.

Graphical displays of the estimated survival curves will be constructed for each primary statistical analysis based on the maximum likelihood estimates of the parameters in the corresponding hazard function. SAS Version 9.4 will be used to perform the statistical analyses (PROCPHREG, PROC NLMIXED) and construct the graphical displays (SASGRAPH).

E.3. Statistical Analyses for Hypothesis 3 and Hypothesis 6

The statistical analyses to address Hypothesis 3 will investigate the relationships between the biomarkers (see *Section D.13.6*) and the time-to-event outcomes. These analyses will be exploratory in nature because

of the numerous biomarkers and time-to-event outcomes to consider.

A preliminary analysis of the biomarkers will determine if they can discriminate between the AKI participants and the non-AKI participants. Therefore, a linear discriminant analysis will be applied to the biomarker data at the inpatient phase and at the 3-month phase.[133] SAS Version 9.4 will be used to perform the linear discriminant analyses (PROC DISCRIM).

The linear discriminant analysis at the 3-month phase will be relatively straightforward because of the uniform manner in which the biomarkers will be measured across the clinical sites. The challenge to the linear discriminant analysis at the inpatient phase is that, given the nature of the four parent studies to the ASSESS-AKI study, the biomarkers for an AKI participant may be measured prior to the AKI event, during the AKI event, and/or after the AKI event. Thus, it is unlikely that each AKI participant will yield biomarker measurements during each of the pre-AKI, peri-AKI, and post-AKI stages of the inpatient phase of the study. Therefore, three distinct linear discriminant analyses will be applied at the inpatient phase, corresponding to the biomarkers measured during the three distinct stages for the AKI participants (for the non-AKI participants, a specific biomarker that is measured on multiple occasions during the inpatient phase will be averaged). Data imputation for missing biomarker values during the three distinct AKI stages will not be invoked.

For the primary statistical analyses to address Hypothesis 3, we will invoke the hazard regression models described above. The additional feature of these hazard regression models is that the inpatient and 3-month measurements of the biomarkers will be included as regressors. Although the biomarkers for an AKI participant may be measured pre-AKI, peri-AKI, and/or post-AKI during the inpatient phase, only the post-AKI biomarkers during the inpatient phase will be considered for the hazard regression models. Biomarker regressors will be inserted into the most salient regression model for a time-to-event outcome (determined previously in the statistical analyses for Hypothesis 1, Hypothesis 2, Hypothesis 4, and Hypothesis 5) in a stepwise selection manner in order to avoid collinearity problems.

Hypothesis 6 states that “A clinically useful and easily implementable risk score can be developed that integrates information on individual characteristics and/or serum/urine biomarkers to provide robust prognostic information for individuals who experience an episode of AKI.” The challenge to develop such a risk score is to validate a candidate regression model on which the risk score is based. The hazard regression models with the regressors described in *Section E.2* and the biomarkers will be applied to the subset of AKI participants and subjected to a cross-validation process. We will partition the adult AKI participants at the three-month visit into an estimation set (two-thirds) and a validation set (one-third), such that the estimation set will be used for the maximum likelihood estimation of the parameters and the validation set will be used to determine how well the estimation predicts the outcome for each member of the validation set. For example, if the predicted hazard for an individual in the validation set exceeds a critical value (for example, 0.5), then the outcome is predicted to occur for that individual, yielding a prediction score based on the proportion of correct predictions in the validation set. Rather than using this type of prediction score, another possibility is to construct an area-under-the-curve (AUC) of a receiver operating characteristic (ROC) curve for time-to-event outcomes.[130] Although the construction of an ROC AUC score for a time-to-event outcome is complex, it does avoid selecting an arbitrary critical value for the predicted hazard.

We will repeat the process of partitioning the adult AKI participants into an estimation set and a validation set 1,000 times so that we can construct an overall prediction score (or an overall ROC AUC score) for the final regression model.

E.4. Sample Size and Power Considerations

The sample size for the consortium is fixed at 750 adult AKI participants and 750 matched adult non-AKI participants, and 50 pediatric AKI participants and 50 pediatric non-AKI controls, at the 3-month visit. Therefore, the following table (Table 15) displays the effect sizes, expressed in terms of the relative risk that can be detected with 80% statistical power under various assumptions for loss-to-follow-up rates. The table indicates that the sample size of 1,500 adult participants, for addressing a primary hypothesis on the full data set, yields sufficient statistical power for detecting relative risks (RRs) less than 2.0. It is estimated that as many as 40% of the non-AKI participants actually may have a mild form of AKI, i.e., there could be misclassification of some true s as non-AKI participants. On the other hand, many of the AKI participants in the study actually will have a more severe form of AKI. Thus, the event rates for both the non-AKI participants and the AKI participants likely will be higher than anticipated. With respect to Table 15, this means that the latter half of the table with the higher event rates probably is more relevant to the ASSESS-AKI study.

Table 15. ASSESS AKI Effect Sizes That Yield 80% Statistical Power (Based on 1,500 Adult Participants)

Event Rate for AKI Participants	Loss-to-Follow-up Rate		
	10%	15%	20%
10.0%	10.0% vs 5.8% RR = 1.72	10.0% vs 5.7% RR = 1.75	10.0% vs 5.6% RR = 1.79
15.0%	15.0% vs 9.9% RR = 1.52	15.0% vs 9.8% RR = 1.53	15.0% vs 9.7% RR = 1.55
20.0%	20.0% vs 14.2% RR = 1.41	20.0% vs 14.0% RR = 1.43	20.0% vs 13.9% RR = 1.44
25.0%	25.0% vs 18.6% RR = 1.34	25.0% vs 18.5% RR = 1.35	25.0% vs 18.3% RR = 1.37
30.0%	30.0% vs 23.2% RR = 1.29	30.0% vs 23.1% RR = 1.30	30.0% vs 22.9% RR = 1.31

Table 16 displays the effect sizes for the subgroup of 100 children, expressed in terms of the relative risk that can be detected with 80% statistical power under various assumptions for loss-to-follow-up rates. Clearly, the sample size of 100 children is small and only large effect sizes can be detected with 80% statistical power.

Table 16. ASSESS AKI Effect Sizes That Yield 80% Statistical Power (Based on 100 Child Participants)

Event Rate for AKI Participants	Loss-to-Follow-up Rate		
	10%	15%	20%
20.0%	20.0% vs 1.5% RR = 13.3	20.0% vs 1.0% RR = 20.0	20.0% vs 0.75% RR = 26.7
25.0%	25.0% vs 4.0% RR = 6.25	25.0% vs 3.5% RR = 7.14	25.0% vs 3.0% RR = 8.33
30.0%	30.0% vs 7.0% RR = 4.29	30.0% vs 6.5% RR = 4.62	30.0% vs 6.0% RR = 5.00

It is of interest to assess the effect sizes that are detectable with 80% statistical power when subgroup analyses are conducted. Therefore, the following table (Table 17) assumes that one-half of the 1,500 adult participants (750 adults) are available for a subgroup analysis. If the event rate for the AKI participants is 20% or greater, then Table 17 indicates that there is 80% statistical power to detect relative risks of 2.0 or less in these subgroup analyses.

Table 17. ASSESS AKI Effect Sizes That Yield 80% Statistical Power (Based on 750 Adult Participants)

Event Rate for AKI Cases	Loss-to-Follow-up Rate		
	10%	15%	20%
10.0%	10.0% vs 4.4% RR = 2.27	10.0% vs 4.3% RR = 2.33	10.0% vs 4.1% RR = 2.44
15.0%	15.0% vs 8.0% RR = 1.88	15.0% vs 7.9% RR = 1.90	15.0% vs 7.7% RR = 1.95
20.0%	20.0% vs 12.0% RR = 1.67	20.0% vs 11.8% RR = 1.69	20.0% vs 11.6% RR = 1.72
25.0%	25.0% vs 16.2% RR = 1.54	25.0% vs 16.0% RR = 1.56	25.0% vs 15.8% RR = 1.58
30.0%	30.0% vs 20.6% RR = 1.46	30.0% vs 20.4% RR = 1.47	30.0% vs 20.1% RR = 1.49

F. INITIAL ANCILLARY STUDY PROPOSALS

Investigators at the ASSESS-AKI CRCs will pursue several initial ancillary study proposals to expand our ability to address key questions that are not currently covered in the core protocol. These include but are not limited to:

- Expanded recruitment of participants with more severe AKI
- Expanded set of follow-up non-invasive cardiovascular/vascular function measures
- Expanded set of serum and urine biomarkers to evaluate association with renal, cardiovascular, and patient-centered outcomes

G. STUDY MANAGEMENT

G.1. Steering Committee (SC)

The Consortium has a SC, which is the main governing body to develop and direct its activities. The six voting members include the four Principal Investigators (PI) of the Clinical Research Centers (CRCs), the PI of the Data Coordinating Center (DCC), the Study Chair, and the Project Scientist from the NIDDK. Co-Investigators and other officials from the National Institutes of Health (NIH) NIDDK may participate in SC activities, but they will not have voting privileges unless the SC decides otherwise. The Study Chair is selected by the NIDDK and is not a PI of one of the CRCs. Responsibilities of the committee include: identifying research topics; selecting topics for investigation; setting priorities for studies to implement; designing studies and developing protocols to submit to the External Expert Panel (EEP); facilitating the conduct and monitoring of the studies, participating in analysis and interpretation of data; assuring that the study results are reported in the scientific literature in a timely manner; and ensuring compliance with the Consortium policies and procedures.

The SC convenes bimonthly via teleconferences and meets at least quarterly to accommodate the timely development of protocols in the Baltimore MD/ metropolitan Washington DC area. The SC operates with standing committees as needed to enhance its effectiveness and includes at a minimum:

- Quality Control Committee
- Biomarker Partners Committee
- Coordinators Committee, which transitioned from the Forms Committee
- Subcommittees
    - Event Adjudication Committee
    - Ancillary Studies Committee
    - Presentation and Publications Committee

G.2. Study Committees and Subcommittees

G.2.1. Quality Control Committee (QCC)

The QCC of ASSESS-AKI develops the standards for data collection, procedures, and laboratory tests used in ASSESS-AKI and evaluates appropriate adherence to them during performance of each protocol. Specific responsibilities include but are not limited to: developing standard data forms, recommending certification requirements for study personnel, monitoring CRC performance using quality metrics developed in coordination with the DCC, recommending changes to improve implementation and performance, reviewing protocol violations, analyzing and interpreting data (includes participation in chart reviews), and planning and conducting site visits, if serious problems are noted at a given CRC.

G.2.2. Biomarker Partners Committee (BPC)

The BPC identifies partners in the scientific and industrial community who will assist with biomarker measurements on the samples collected by the ASSESS-AKI study. The NIDDK Project Scientist, DCC PI, and an investigator from each CRC comprise the BPC. Responsibilities of the BPC include identification of core list of biomarkers that will be measured and the quantities needed, identification of potential biomarkers, reviewing the RFPs from central lab applicants and biomarker partners, and reviewing proposed ancillary studies that request biospecimens before the proposal is recommended to the SC. In addition, the BPC establishes protocols for data/sample flow in the study.

G.2.3. Coordinator Committee (CC)/ Forms Committee

The Forms Committee develops the standard data collection forms for adult and pediatric participants for review and approval by the QCC. Chair of the Forms Committee is the DCC Scientific Coordinator. Forms Committee membership consists of the DCC team (Scientific Coordinator and Data Management and Research Computing representatives), at least one coordinator from each CRC, and CRC site investigators. Responsibilities include developing standard data collection forms, pilot-testing the pre-approved forms using chart reviews and interviews, proposing form changes, and presenting the forms to the QCC for review and approval. The Forms Committee transitioned into the Coordinators Committee once the forms were finalized.

The Coordinators Committee serves as a forum to review any protocol, form, or MOP changes and provide updates on Steering Committee and other ASSESS-AKI Committee decisions. The Coordinator Committee consists of the DCC team (Scientific Coordinator and Data Management representatives) and at least one coordinator from each CRC site. The Coordinator Committee identifies any protocol, forms, and/or MOP issues at the site level. Unresolved issues will be brought to the attention of the SC or the QCC.

G.2.4. Event Adjudication Committee (EAC)

The Event Adjudication Committee will be comprised of physician investigators from each of the CRCs who will be responsible for centrally adjudicating potential outcomes events based on review of relevant medical records. At least two Committee members will review each potential clinical event and follow standardized criteria consistent with the approach being used in other prospective renal cohort studies (e.g., CRIC).[95]

G.2.5. Ancillary Studies Committee (ASC)

The ASC and the SC must review and approve all proposed ancillary studies before their inception or submission of a proposal for external funding consideration. If samples are requested, the BPC must also review and approve the ancillary study proposal. The Ancillary Studies Committee (ASC) is chaired by the Chair of the ASSESS-AKI Steering Committee.

An ancillary study is one based on information derived from ASSESS-AKI Study participants in an investigation or analysis that is relevant to, yet not described in, the ASSESS-AKI Study protocol, and that derives support from non-ASSESS-AKI funds. An ancillary study may propose the collection of additional data not collected or analyzed as part of the routine ASSESS-AKI Study data set. Ancillary studies may be

submitted by the investigators within the Consortium or by investigators without a prior relationship to the Consortium. Ancillary studies require external (non-ASSESS-AKI) funding to cover all associated costs.

The major responsibilities of the ASC are to review all proposed ancillary studies and to assess the merit of each proposed study, advantages and disadvantages with respect to ASSESS-AKI goals, burden of the proposed measurement collection on the ASSESS-AKI study, sites, and participants, and suitability for endorsement by ASSESS-AKI SC.

ASC develops policies relating to the distribution of data and biological specimens generated by ASSESS-AKI to non-ASSESS-AKI investigators. Those policies are approved by the voting members of the SC. The ASC evaluates and makes recommendations for use of data or biologicals by specific outside (i.e. non-ASSESS-AKI) investigators. Decisions in this regard are to be recommended to the SC for final decision by voting members.

All policies and recommendations need to be in accordance with NIH and federal guidelines, and when possible in accordance with individual institutional guidelines. Policies and recommendations (internal and external) will be dictated by the nature of the informed consents signed by the participants.

G.2.6. Presentation and Publication Committee (Pub-Pres C)

The purpose of the Publications and Presentation Committee (Pub-Pres C) is to ensure timely completion of manuscripts and presentations, equitable access to authorship, and adherence to the ASSESS-AKI Study Publication and Presentation Policy.

G.3. External Expert Panel (EEP)

G.3.1. Purpose

Given the multi-site structure of the Consortium, the NIDDK has formed an EEP. The EEP functions in an advisory capacity to the Director of the Division of Kidney, Urologic and Hematologic Diseases of the NIDDK. The EEP may propose modifications to the ASSESS AKI study and will monitor study progress and patient safety issues. One of the functions of the EEP is to review the objectives, hypotheses, design, and analytic plans developed by the ASSESS AKI. The EEP can suggest recommendations or propose modifications for the protocol to the NIDDK. The EEP will not participate in the conduct of research or publication of results of the work performed by the SC or CRCs.

The DCC, along with selected CRC investigators, will present the protocol and results of analyses to the EEP. The EEP will review study performance and quality of the study data. NIDDK staff will serve as the Secretary of the EEP. Summary reports of the EEP meetings prepared by NIDDK staff will be distributed to each Consortium PI by the DCC within 30 days following each EEP meeting. These summary reports include a statement that an EEP review of the data and outcomes across all CRCs took place on a given date; and the EEP's summary comments with respect to study progress and/or potential suggested protocol modifications. The DCC will forward these summary reports to its IRB, and the Consortium PIs will be required to forward them to their local IRBs. Regarding the protocol process, the EEP will evaluate the protocol's integrity, protection of patients' study rights, and potential risks.

G.3.2. Membership

The EEP is selected by the NIDDK. The EEP includes individuals with expertise in nephrology, AKI, cardiovascular disease, biomarker biology, biostatistics, and bioethics and consumer advocacy as necessary. No EEP member is associated with the institutions represented by the DCC and the CRCs.

G.3.3. Schedule for Interaction with SC

The EEP will meet with members of the SC at least annually to present results of the study and to assess study performance and quality of the study data.

G.4. Participating Laboratories

Participating laboratories will consist of central laboratories (University of Minnesota) for measurement of core clinical parameters and novel biomarkers and all the local laboratories at the clinical sites (Kaiser Permanente of Northern California, Vanderbilt University, Yale University, University of Washington, London Health Sciences Center (Ontario), University of Cincinnati Children's Hospital, and Montreal Children's Hospital). Measurement of novel biomarkers will be conducted at the ASSESS central laboratory (University of Minnesota), University of Vermont Laboratory of Clinical Biochemistry Research, and the W.M. Keck Foundation Biotechnology Resource Laboratory.

G.5. Reading Centers

The ASSESS AKI central ECG reading center, Wake Forest (EPICARE), will be contracted with to review all ECGs obtained through the study visits and as needed, to facilitate event adjudication for acute coronary syndromes.

G.6. Study Policies

G.6.1. Ancillary Study Policy

The final policy is available in section 5.I. of the General MOP and is consistent with current NIH guidelines.

G.6.2. Publication and Presentations Policy

The final policy regarding publication and presentations policy is available in section 5.L. of the General MOP and is consistent with current NIH guidelines.

G.6.3. Access to Study Data and Specimens

The final policy regarding access to study data and specimens is available in section 5.M. of the General MOP and is consistent with current NIH guidelines.

G.6.4. Intellectual Property

The final policy regarding intellectual property will be developed and be consistent with current NIH guidelines.

G.6.5. Duality of Interest

G.6.5.1. *General Principles*

The validity of research studies depends on investigator objectivity, and the general acceptance of research study results depends on the perception of investigator objectivity. Dualities of interest can be critical to both of these considerations since they can lead to or create the perception of bias. Dualities of interest may arise from interactions between investigators/research personnel and organizations such as private corporations, scientific or medical societies, and non-profit groups. Accordingly, the ASSESS-AKI Consortium must ensure that interactions and/or relationships with industry or other groups outside of the study organization do not influence (or appear to influence) the objectivity of the ASSESS-AKI decision making processes.

Loss of objectivity can result from financial and other factors. For example, scientific judgment can be affected by considerations of career standing. Not only can objectivity be diminished by such situations, but also commitment to the research endeavor.

Dualities of interest can involve a research organization rather than an individual investigator. Financial or other interests can conceivably affect the objectivity of a research group. This type of potential duality of interest must also be considered in the conduct of research studies.

Dualities of interest are not prohibited; however, it is imperative that real, possible, or potential dualities be declared to ensure objectivity and maintenance of individual and organizational integrity. While the process utilized to develop ASSESS-AKI studies should diffuse the potential impact of any duality that exists for an individual member of the ASSESS-AKI Consortium, it is the position of ASSESS-AKI Consortium that disclosure of any duality that exists or arises for a member will add assurance that ASSESS-AKI studies have been conducted in a fair and scientifically sound manner, devoid of inappropriate influences or the appearance of inappropriate influences. In order to attain further objectivity, the ASSESS-AKI Consortium will require management of dualities of interest when it is deemed necessary.

G.6.5.2. *Definitions*

Duality of Interest means a circumstance in which financial or other considerations can affect scientific objectivity or commitment to a research endeavor.

Research is a systematic investigation designed to develop or contribute to generalizable knowledge.

Investigator means principal investigator, co-investigator, and any other person at the institution who is responsible for the design, conduct or reporting of research. For the purposes of financial interest, "investigator" includes the investigator's spouse and dependent children.

Study-related entity means an entity with an active or potential interest in the conduct or outcome of an ASSESS-AKI Consortium study because:

a. a drug, biological, device or other product ("product") of the entity is a topic of research in the ASSESS-AKI Consortium study

b. a drug, biological, device or other product of the entity is a direct alternative or substitute for the product that is the topic of research by a Consortium study, or;

c. a drug, biological, device or other product of the entity is being used in the study (e.g., as a tool or as an adjunct, but not as a primary study drug) at a time in its scientific or commercial development that would play a substantial role in its commercial viability and success).

d. the impact of the use of the enterprise's product by the ASSESS-AKI or the outcome of ASSESS-AKI research may reasonably be expected to have a very significant impact upon the value of an investment

Financial interest means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria). It does not include indirect financial interest through broadly diversified instruments, e.g., in broadly diversified mutual funds and retirement plans.

Significant financial interest means financial interest in a business enterprise or entity if:

a. the value of the interests plus payments for services (but not the reimbursement of reasonable directly incurred costs) exceeds $10,000 per annum, or;

b. equity interest exceeds $25,000 (e.g., stocks, stock options, or other ownership interests); intellectual property rights (e.g., patents, copyrights, and royalties from such rights),

Other significant relationships with a study-related entity include:

a. research, training or other support from the entity for an ASSESS-AKI investigator, or in which the ASSESS-AKI investigator is involved, or over which the ASSESS-AKI investigator has control, responsibility for conduct, responsibility for making appointments, or the like, even if funding is not to the ASSESS-AKI investigator;

b. possible other relationships in which there is or seems to be dependency relationship of the ASSESS-AKI investigator to the study-related entity;

c. current or proposed participation in a clinical trial funded by non-NIH sources, which addresses a research question with close similarity to a proposed ASSESS-AKI Consortium study.

G.6.5.3. *Policy*

This policy and its definitions (e.g., financial interest, significant financial interest, other significant relationship, and study-related entity) shall be public information and shall refer to interests/relationships over the two calendar years prior to disclosure.

The existence (but not the amount or details) of any financial interest, any significant financial interest, and any other significant relationship of any ASSSESS-AKI Consortium investigator or any exception to the standard policy in any ASSESS-AKI Consortium study shall be public information. The existence of a

significant financial interest and other significant relationships shall routinely be acknowledged in publications or as otherwise required.

A master list including financial interests, significant financial interests, or other significant relationships will be prepared by company name listing all the PI/co-investigators who have involvements with the individual companies.

Recommendations concerning potential conflicts of interest will be the responsibility of the ASSESS-AKI Steering Committee (SC), which is comprised of the four ASSESS-AKI Principal Investigators, the Steering Committee Chair, and the NIDDK Steering Committee Members. The Chair will supervise the review of disclosure documents and will oversee discussion and adjudication of potential conflicts by the ASSESS-AKI Principal Investigators. Upon review of a particular potential conflict of interest, the SC PIs will decide the level of participation and involvement the individual with the potential conflict may have with a particular study, on an individual case basis.

In general, no member of the ASSESS-AKI Steering Committee or co-investigator at a given center shall participate as an investigator or as a co-author in a for-profit company study with a research question similar to the one undertaken by the ASSESS-AKI. Permission by the Steering Committee to participate in such a study by an investigator with a potential conflict may be given and shall be public information.

Steering Committee members shall neither review nor rule on potential conflicts from their own ASSESS-AKI center.

In general, a member of the Steering Committee who has no potential conflict of interest with a study-related entity should conduct negotiations with a particular company (e.g. to obtain drug for a study, or to acquire equipment for the ASSESS-AKI). A person with a potential conflict should not have any involvement with certain entities (e.g., a biomarker company) regarding the specific project (e.g., negotiations for supplies) without the permission of the Steering Committee. The Steering Committee can waive this restriction based on the nature of the study, the role of the investigator, and the type of involvement.

Anyone with a significant financial interest, or other significant relationship (as defined above) must have at least one non-conflicted Co-PI involved with any study in which the individual with the conflict is permitted (by the Steering Committee) to participate. The Steering Committee can waive this restriction based on the nature of the study and the role of the investigator.

Permission by the Steering Committee to participate in a study by an investigator with a potential conflict shall be public information.

Relationships of investigators with study-related entities (and representatives of these entities) shall also adhere to the following principles:

ASSESS-AKI Consortium-related activities shall be discussed only as needed by the study and in the role of, or on behalf of, the ASSESS-AKI activity, but never in the context of other discussions, relationships, or interest that the investigator and that entity may have.

ASSESS-AKI study protocol and policies relating to the release of information dictate the confidentiality of

non-publicly released information, as well as the release of certain confidential information to certain interested entities. Investigators must adhere to these policies. Except in a formal role, on behalf of the study, they must scrupulously avoid transmitting information to any entities that have interest in the study and they must be particularly scrupulous in avoiding such release of information to an entity in which the investigator has a financial interest.

To avoid conflicts of interest, every attempt will be made to offer companies participation on an open basis without specific product selection unless a specific product is deemed preferable by the group for patient safety, efficacy or convenience. If one product is indeed deemed preferable by vote of the Steering Committee, then a careful analysis for potential conflicts of interest will take place. Investigators must be cognizant of and adhere to federal regulations on the prohibition of "insider trading."

G.6.5.4. *Process*

Conflict of interest forms will be completed twice yearly. Each investigator is responsible for identifying for review those related financial interests that meet criteria (a) or (b) under significant financial interest, and those which, although not meeting these criteria, raise issues which might reasonably be expected to raise concerns. Any other significant relationships with study-related entities must be described at least briefly, but in sufficient detail so that their acceptability can be assessed.

The potential for conflict of interest will be reviewed and whenever new protocols or products, or relationships with new entities are considered by the ASSESS-AKI Consortium, or if an investigator develops or terminates an ASSESS-AKI significant (or potentially significant) financial interest or such interest changes. Potential conflicts of interest involving immediate family members of the participating investigators should also be identified.

Twice annually, and at the beginning of any new protocol, PI/co-investigators will notify the Steering Committee of any changes in their disclosure statement, and any potential conflict of interest will be reviewed by the Steering Committee.

The principal investigator at each ASSESS-AKI Clinical Research Center shall be responsible for transmitting to the Data Coordinating Center not only his or her own disclosure statement, but those of others at his or her institution that may fulfill the criteria of the participating investigator. The disclosure material must include a list of study-related entities in which there is a financial interest or with which there is another significant relationship, the basis and nature of the interest or relationship, and its classification as "significant financial interest" or "financial interest" and/or "other significant relationship." Steering Committee members shall neither review nor rule on potential conflicts from their own ASSESS-AKI center. In general, if the committee feels that there is a potential conflict of interest, the investigator involved will recuse himself or herself from all discussions and decisions pertaining to the ASSESS-AKI protocol.

The investigator is responsible for identifying for review any related financial interests that do not meet specific criteria under significant financial interest or other significant relationship (particularly other significant relationship criterion c), but for which reasonable persons might have differing judgments as to meeting these criteria. Any other significant relationships with study-related entities must be described at

least briefly, but in sufficient detail so that their acceptability can be assessed.

Exceptions may be made in circumstances where both the substance and the appearance of the conflict are each sufficiently small and benefits to the study and the public outweigh these factors. If an exception is sought to this stated policy, the basis for it must be indicated. Participation by exception to standard policy shall be public information.

If the Steering Committee permits an investigator with a potential significant conflict to participate in discussions and decisions regarding a specific protocol and entity, the potential conflict shall be announced to and reviewed with the Steering Committee before the discussions commence.

The recommendations of the ASSESS-AKI Steering Committee shall be conveyed by the Chair to the NIDDK. In granting a waiver to the policy, the Chair and/or the NIDDK may seek independent review and advice from outside sources, if that process is deemed necessary.

Disclosure statements shall be kept within a secure file at the Consortium's Data Coordinating Center following review by the Board.

ASSESS-AKI Consortium publications should have a written disclosure statement, along the lines currently required by the New England Journal of Medicine.

G.7. Clinical Research Center and Data Coordinating Center Responsibilities

The PI at each of the CRCs bears overall responsibility for that center's participation in the ASSESS-AKI Consortium. The PI hires and supervises relevant personnel which could include Co-Investigators, oversees ASSESS-AKI data collection, participates in quality assurance measures, prepares budgets and annual reports, obtains IRB approval for ASSESS-AKI protocols, and represents the CRC on the SC.

A Project Manager is at each of the CRCs and functions under the supervision of the PI. The Project Manager shall be responsible for all study operations of the respective CRC. The Project Manager establishes procedures to ensure adherence to protocols and to assure data of high quality, participates in Project Manager meetings and phone conferences, serves as the primary contact between the CRC and the DCC, attends SC meetings, and participates in protocol subcommittees and site visits as necessary.

The DCC at the Pennsylvania State University, Hershey, PA plays a key role in developing and facilitating study protocols. It is responsible for statistical planning and accumulation of quality data from the CRCs. The staff members of the DCC assist in the development of protocols and in preparing timetables for operation of studies, format data collection forms and manuals of operation, determine design, sampling and randomization schemes, assist in defining primary and secondary outcomes in the protocols, execute statistical analyses of study data, and serve as a central repository for data generated from the CRCs. The DCC plans for any subcontracts for chemical analysis and assists in preparation and masking of medications. The DCC monitors participant recruitment and provides recruitment reports to the CRCs, the NIDDK, and the EEP on a regular schedule.

In conjunction with the QCC, the DCC develops procedures for quality control, training, and certification of CRC staff. Quality and quantity of data from the CRCs is monitored and reported by the DCC to the CRCs and the SC. In addition, the DCC:

- Prepares protocols for submission to the SC and prepares confidential reports for the EEP as well as interim and final analyses and other specific statistical analyses and reports.
- Supports manuscript preparation through data analysis, statistical consultation, and editorial tasks.
- Supports ASSESS-AKI-related activities through the coordination of all meetings and phone conferences and the dissemination of agendas and action items.

The PI of the DCC is a voting member of the SC. Additional DCC staff includes Co-Investigators, Scientific Coordinator, Data Managers, Programmers, and Data Clerks. DCC staff may author or serve as coauthors of publications from the clinical trials.

G.8. Quality Assurance/Quality Control Activities

G.8.1. Personnel Training

Consistency in performing protocol-defined procedures and recording study data strengthens the ability to achieve scientifically accurate outcomes. Therefore, it is crucial that research staff are trained and certified in all Consortium procedures. The DCC designs sessions to train the CRC staff in skills necessary to collect, record, and process protocol data, such as using the secure Consortium web site, recording data on the paper data collection forms, using the web-based data management system, and performing all Consortium procedures. The DCC will develop a two-day protocol training session at the DCC as well as training via telephone conferences, or web-based training using WebEx or CONNECT conferencing and presentation technology. DCC will create electronic, self-paced tutorials to teach research staff how to use the data management system modules. Macromedia Captivate software automatically records all onscreen actions, instantly creating an interactive Flash simulation that can be enhanced and edited using text captions, narration, images, and audio. The research staff can use these tutorials as refreshers or tools for training new staff at their sites.

G.8.2. Study Monitoring

The DCC team works with the SC and QCC to develop standard procedures for collecting protocol data in order to reduce data variability within and across the clinical sites. These procedures are detailed in the General Manual of Operations (General MOP).

G.8.3. Other Quality Assurance Activities

The QCC is responsible for identifying the procedures that the CRC staff is assessed for competency prior to collecting protocol data. The DCC collaborates with the QCC in defining the criteria for certification and de-certification (if applicable). Certification procedures may include reading a MOP, passing a written exam, and/or demonstrating hands-on competency. The DCC recommends mandatory protocol-specific certification for all research staff. Project management staff electronically record and track the status of CRC staff certifications using a certification application developed by the DCC. All Consortium personnel

are able to access real-time certification status reports from the secure web site. CRC staff is required to record their unique ID number on each data collection form they complete. The DCC programs electronic error checks that cross-check these numbers against the data in the certification table. This identifies CRC staff that (1) are certified, (2) have completed procedures but have not been certified, or (3) have been de-certified to perform a procedure or collect data.

G.9. Data Management

G.9.1. Electronic Data Management Systems

The processes and checks built into this system are effective in maintaining high data quality. The DCC designs separate data collection forms based on who is collecting the data, where the data are being collected, and when the data are collected. The DCC also designs forms to collect cumulative repeating information such as adverse events and medication usage. The CRCs complete the information required in standardized form headers (the unique participant ID, the date of collection, and the identification number of the staff recording or collecting the data) and record protocol data onto the corresponding data collection forms. There may be some Consortium data that can be entered real-time into the data management application where error checks and pre-defined skip patterns can be programmed while other settings may require research staff to record data on paper data collection forms for entry at a later time. Using the DBMS application, the CRCs register each new participant into the Consortium registry. The registry assigns a unique identification number to the participant, linking a participant's data to the parent protocols.

After the CRCs record the data on all the forms in a pre-defined packet for a participant, they enter the data using the web-based data entry module within the DBMS (Figure 14). They are prevented from entering values that violate the database constraints defined for each variable. Clear messages alert them to what a valid value should be. After the CRC has entered the data for all the forms for a specific participant in a packet, a number of error checking rules are executed real-time resulting in an entry error report that can be viewed and/or printed using a browser. The CRC can choose to fix the errors while in the entry module or make the changes at a later time using an editor module. The DCC currently distributes about 90% of all possible error checks during CRC data entry. In cases where one or more values are identified as errors but are confirmed correct, the CRCs can access a module to mark the error(s) as "unresolvable," providing a comment as to why the value is correct.

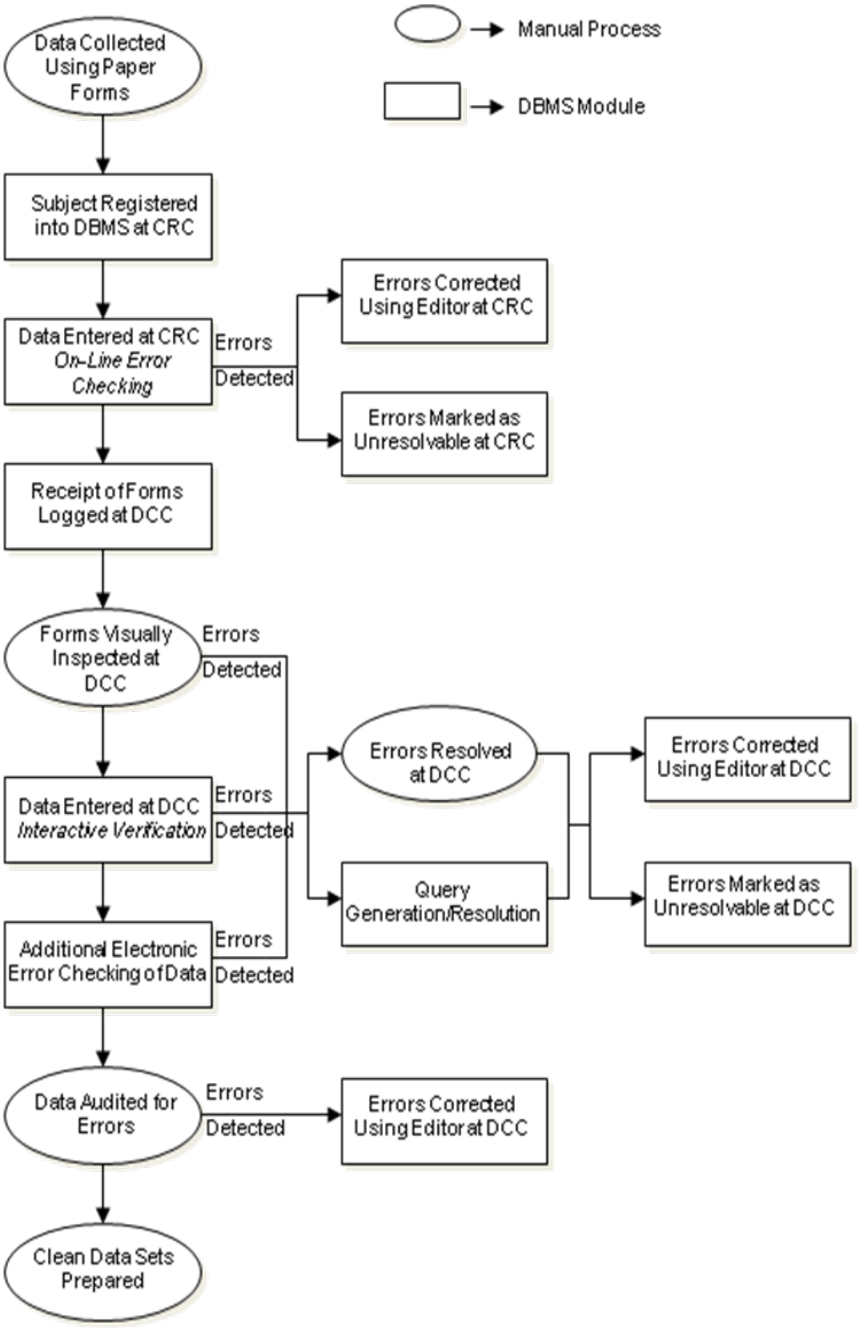


Figure 14. Proposed Data flow for the ASSESS-AKI Consortium

Following data entry and editing, the CRCs are required to photocopy all the forms for their records and forward the original data collection forms, along with any required source documents such as laboratory reports, to the DCC. The forms are logged in the data management application with the date of receipt. DCC staff scans the forms creating index variables for each form in order to store and retrieve the images (via a web link) during the data problem resolution process. Data management staff visually inspects the forms to identify problems that cannot be discovered electronically, such as forms from two different

participants together in the same packet or an incorrect transcription of values from generated reports to the data collection forms. The DCC performs a second verification entry of pre-selected forms. The verification process is interactive by alerting the data entry clerk to a discrepancy between his/her entry and what was entered at the CRCs. The entry clerk can change the value or leave the field blank for later resolution by a data manager. The DCC executes additional error checks in a batch format every evening to identify more complex errors based on illogical or inconsistent values across different time points or among data residing in different database tables. The data manager queries the CRCs using an error-tracking module to resolve all problems not previously resolved at the CRCs or found during batch validation or visual inspection at the DCC. The data manager edits the data accordingly based on the CRC's response to the query.

G.9.2. Security

Data transmissions over the network are encrypted using a 128-bit Secure Sockets Layer (SSL) encryption standard, for which the DCC has its own security certificate. The SSL protocol provides data security layered between application protocols (such as Hypertext Transfer Protocol (HTTP) and Transfer Control Protocol/Internet Protocol (TCP/IP). This security protocol provides data encryption, server authentication, message integrity, and client authentication for a TCP/IP connection.

Computer network security is maintained through network hardware, user authentication, and user roles within the database. All computers connect through an Internet firewall that prevents unauthorized users from gaining access to the internal network structure. The firewall protects the computer network, and DCC staff members are experienced with the requirements for database access through an active firewall. The local firewall is monitored continuously and equipment logs are reviewed daily for abnormalities or security issues. DCC staff members work closely with CRC information technology specialists to ensure the CRC can connect to the research database application. DCC uses both the Sun Java System Web Server with SSL certificate-level authentication and Oracle database authentication with individual username/password and role information stored in the database. The database roles facilitate or restrict access to specific areas related to an individual's position, duties, and responsibilities within the Consortium and the Sun Java System Web Server combined with the Oracle database management system constitute an advanced security model that supports multiple types of authentication. The database application and supporting network meet the security requirements of HIPAA.

G.9.3. Record Retention

Assuming that all relevant data from the CRCs have been submitted to the DCC and entered into the study database, the National Institutes of Health (NIH) have no formal policy regarding the storage of subject files at specific CRCs within the ASSESS Consortium. However, despite the absence of a formal policy, the NIH has formulated a few recommendations for storing subject files at clinical centers:

- Clinical study records are considered medical records and should be stored under the applicable guidelines of state and local regulations.

- Every attempt should be made to store records within each center's allocated space in the event that an approved federal agency would request an audited account of the records in the future.

G.9.4. Standard Reports

The DCC will create a number of real-time reports to summarize the performance of the CRCs (individually and as a whole) and the DCC in implementing SC specifications and expectations and producing a quality database for statistical analysis. Members of the Consortium may access these reports at the password-protected web site. These include: (1) accrual, to monitor the recruitment and flow of participants in the protocol according to specified goals; (2) certification, detailing the certification status of every person at the CRCs for each procedure and data collection process; (3) protocol violations, listing departures from Consortium procedures that pose a threat to the integrity of the research data; protocol deviations, listing departures from procedures that do not adversely affect the integrity of the data, and protocol exceptions, listing exceptions to eligibility criteria permitted by the SC; (4) quality control, summarizing quality control measures such as the number of missed data collection points or forms and the number of data collection points occurring outside of defined windows; (5) data submission timeliness, measuring the timeliness of the CRCs in entering the data and submitting it to the DCC for verification; (6) CRC query performance, listing such measures as the number of queries sent to each CRC, the number of outstanding queries, and the average time between the date of the query and the response by the CRC; and (7) DCC timeliness, listing the average number of days between receipt of the data collection forms from the CRC and verification at the DCC. The CRCs and DCC will have access to other reports that provide data processing information such as a list of the validation errors generated during first entry, the data corrections submitted by the CRCs and the DCC, and the queries sent by the DCC to the CRCs. These reports will facilitate data clean-up.

The DCC also will create a report to monitor the number and types of validation errors and queries by data collection form type in order to identify areas where the CRCs are having difficulty in recording or entering data. This, like the data audits, will give the DCC information as to where to retrain CRC staff to improve data quality or where modifications should be made to the data collection forms. In addition, the DCC will closely monitor the number of entry errors that the CRCs are marking as “unresolvable.” Data management staff will review these on a regular basis and contact the CRCs if they are inappropriately marking these errors as “unresolvable.” The data management staff will create reports to monitor the activity of data processing within the DCC as well as forecast the flow of data receipt at the DCC. These figures will help identify workflow issues at the DCC as well as problem areas that should be addressed.

G.9.5. ASSESS-AKI Website Maintenance

Back-ups of the Consortium databases occur every night, with DCC user data backed up incrementally Monday through Thursday and complete back-ups on Friday. Archival back-ups, stored indefinitely, are cut on the last weekend of every month. All back-up data are stored in a secure off-site location in accordance with current disaster preparedness planning directives. The number and variety of back-ups ensure ample data redundancy and protection. The DCC maintains a user helpdesk to assist each CRC with computer hardware and software problems. A CRC may contact the helpdesk via a web page template, e-mail, or the Consortium-dedicated phone line to initiate correction of a problem at the CRC. The helpdesk phone line has voicemail for after-hours problem reporting.

G.10. Data Access

G.10.1. Data, Reports, and Analyses During the Study

During and after a study, reports and analyses will be generated by the DCC in response to requests from the SC, EEP, or NIDDK. Prior to a meeting of the SC or EEP, the group will determine reports to be presented at the meeting. Their requests will be conveyed to the PI at the DCC, who will then oversee the preparation of the reports. For EEP meetings, all reports will be presented only to members of that committee and will be treated with the strictest confidentiality, including collecting all copies of the reports at the end of the EEP meeting.

Routine reports of descriptive data (e.g., descriptive statistics of baseline data) may be presented to the SC as requested during the study. Statistical analyses of study results will be performed under the direction of the SC.

G.10.2. Database Availability After the Study

While the study is underway and primary publications are being developed, access to the database will be restricted to certain personnel at the DCC. Within a period of time to be determined after publication of the primary results, a documented copy of the final study database will be made available to all CRCs. Awardees will retain custody of and have primary rights to the data developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies. The collaborative protocol and governance policies will call for the continued submission of data centrally to the coordinating center for a collaborative database; the submittal of copies of the collaborative data sets to each PI upon completion of the study; procedures for data analysis, reporting and publication; and procedures to protect and ensure the privacy of medical and genetic data and records of individuals. The NIDDK Project Scientist, on behalf of the NIDDK, will have the same access, privileges and responsibilities regarding the collaborative data as the other members of the SC. Awardees are encouraged to publish and to publicly release and disseminate results, data and other products of the study, concordant with the study protocol and governance and the approved plan for making data and materials available to the scientific community and the NIDDK. However, during or within the period beyond the end date of the project period of NIDDK support, unpublished data or products are to be made available to any third party only with the approval of the SC. Upon completion of the project, the DCC is expected to put all study intervention materials and procedure manuals into the public domain and/or make them available to other investigators, according to the approved plan for making data and materials available to the scientific community and the NIDDK, for the conduct of research at no charge other than the costs of reproduction and distribution.

H. Human Subjects Consideration

H.1. Clinical Management of Participants

H.1.1. Clinical Alerts

Medical alerts will be defined to identify and report significant medical findings that arise during participation in the ASSESS-AKI Study to the participant and his/her health care provider. Participants and their providers must be notified immediately if potentially serious medical problems are identified during any of the examinations. Urgent conditions will be reported as soon as possible after they become evident. Immediate alerts are those associated with a medical emergency and require a prompt response. If this occurs during a participant's scheduled study visit, the investigator is obliged to react to the situation. Immediate alerts will be evaluated by a physician who will determine the appropriate disposition. The final set of alerts will be developed prior to initiation of recruitment. Our initial approach is modeled after the CRIC Study which has multiple overlapping measures. Examples of clinical and laboratory findings for adult participants that might initiate an immediate alert response include: Systolic BP > 180; Diastolic BP > 110, chest pain, severe respiratory distress, acute neurological symptoms, hyper- and hypo-kalemia (≥ 6 mEq/L or < 3.0 mEq/L), Hypo- and hypernatremia (<125 mEq/L or >155 mEq/L), hypo- and hyperglycemia (< 50 mgdL or > 350 mg/dL), hemoglobin < 10 gm/dL, and creatinine doubling from last value.

H.1.2. Transmission of Study Findings and Response Time

As laboratory, physical measures, and other test results become available, they will be sent to participants to provide to their primary treating physicians. Permission to forward this information will be obtained during the consent process at the time of study entry.

In the event of an immediate alert, prompt notification of the participant's physician should be accomplished by telephone, before the participant leaves the clinic. A follow-up letter or email documenting the information discussed by telephone must also be sent to the participant's physician.

H.1.3. Referral for Clinical Care of Participants Lacking a Primary Care Provider

In the event that a participant does not have a primary care provider, the study coordinator at the respective study site will assist the participant in identifying an appropriate primary care provider, if requested.

H.1.4. Standards of Care

Participation in this study will not interfere with the provision of care and it is anticipated that all participants will receive the standard of care appropriate for their kidney disease status and any other co-morbidities.

H.2. Ethical Issues

H.2.1. Potential Risks to Participants

Risks to participants at the CRCs are related to their participation in treatment regimens related to AKI. These risks will be evaluated on a protocol-specific basis. The alternative is not to participate in the study, in which case the participant would receive standard care from his/her usual health care provider. The main potential risk to participants with regard to the DCC is the possibility that a participant's identity may be accidentally disclosed to the DCC. The DCC will be very sensitive to this issue, and if a CRC mistakenly sends the DCC identifying information, then the DCC will blacken the identifying information on the data collection form and immediately notify the CRC of its error.

H.2.2. Risk/Benefit Assessment

There is no guaranteed benefit from participating in ASSESS-AKI. A participant may benefit by receiving a physical examination, laboratory studies, and frequent assessments free of charge. Participants may receive free access to health education and specialist care during the study. Investigators may learn more about the natural history of acute kidney injury and determine the best interventions to use in patients. Participation in these studies may ultimately help in the treatment of acute and chronic kidney disease and provide knowledge about the phenoptypes and genotypes that predict favorable and unfavorable responses to medication, medical devices, cell therapies, gene therapies, surgeries, etc. These benefits appear to outweigh any minimal risk of breach of confidentiality.

H.2.3. Gender and Minority Inclusion

The DCC will ensure that the protocol includes a targeted enrollment form for gender and minority representation, and that the form is submitted to the NIH for approval. It is expected that a typical study will seek to enroll one-half females and one-half males, and one-third minorities (with the distribution dependent on the racial and ethnic diversity of the participating CRCs).

The protocol enumerates the criteria for participation based on the interventions proposed and contains specific criteria and rationale for participant selection. In general, this protocol does not exclude individuals of any sex/gender or racial/ethnic group. Dates of enrollment are designated in each individually developed protocol. It is not expected that any unusual outreach activities will be necessary to enroll women and minorities into the protocols. Analyses are planned routinely to detect differences in treatment effects within subgroups, such as genders and racial/ethnic groups. Although subgroup analyses may not have high statistical power because of small sample sizes, they identify groups that may particularly benefit, or be at risk of harm, from the study intervention(s).

H.2.4. Informed Consent

The CRCs are responsible for recruiting participants and obtaining informed or surrogate consents. The DCC is responsible for assuring that each local IRB has approved the protocol for a Consortium study and the procedures for recruitment, and has reviewed and approved the informed consent document. A Consortium study cannot begin at a CRC until that CRCs has submitted IRB approval(s) to the DCC.

Informed and surrogate consent documents and signatures are retained at the CRCs. The CRCs will recruit participants by adhering to HIPAA regulations from “standing” populations at the CRCs by research, pharmacy and disease management databases, by referral from collaborating physicians, and by advertisement (flyers, brochures, posters, news media, etc). The DCC will provide real-time accrual reports for each CRC at the password-protected Consortium web site, listing the enrolled participants and any reasons for exclusion during the assessment/characterization run-in periods. This routine monitoring allows for early identification and resolution of potential problems during the recruitment phase. The recruitment duration will be specified for each study.

The lead investigator for each Consortium study, in conjunction with the SC, will develop a template for the informed/surrogate consent documents. The goal of the consent process will be to establish and maintain procedures aimed at providing each potential participant with sufficient time and information to make informed decisions about participation in a Consortium study. The cornerstone for research on human beings is voluntary consent based on accurate information. The consent process is one of the more important participant-investigator activities because, if done properly, it serves not only to inform but also to bond the participant and the CRC. Moreover, the consent process that will be employed in the Consortium will be a continual process with continued education of participants about the study. Amendments to consent and re-consenting may be needed as additional important information becomes known to the Consortium. HIPAA authorization language will be included, as necessary, in the confidentiality section of the informed consent form.

H.2.5. Confidentiality

Extensive procedures are in place to protect participant confidentiality, including transmission of all study data without linkage to personal identifiers. If participant confidentiality is compromised, the DCC will treat it as a high-level protocol violation and inform the NIH, the Consortium QCC, and the CRC responsible for the transgression.

All medical interactions, data collection, and treatments will be maintained with confidentiality and professionalism. No information ever will be released that could identify an individual participant. All participants will be closely monitored for disease control and appropriate adjustments made in a timely manner according to protocol management. Procedures will be implemented in each Consortium protocol for the protection of human subjects: creation of understandable consent documents; adherence to a formal consent process; linkage of a participant's protected health information by a study ID number and only those HIPAA identifiers necessary to perform appropriate analyses; and procedures for identifying, reporting, and reviewing of adverse events. Any participant who withdraws consent to participate, or for whom the study physician determines that continuation in the study would not be in the best interest of the participant, will be assigned withdrawal status.

APPENDIX

Appendix I. ASSESS AKI Novel Biomarker Measurements – Adults

ASSESS AKI Novel Biomarker Measurements - **Adults** 10/03/2019

Core Measurements	Status	Assay site	V0	V3M	Annually	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
Serum (+ V0 samples are plasma)										
Creatinine	Complete	UMinn		X	X	7,420 V3M=1603 V12M=1334 V24M=1203 V36M=1105 V48M=983 V60M=700 V72M=353 V84M=139	7,420 V3M=1603 V12M=1334 V24M=1203 V36M=1105 V48M=983 V60M=700 (1) V72M=353 V84M=139	Roche ModP (Dec 2009-2013); Roche Cobas 6000 (Jan 2014-present)	Parent	Started Dec 2009
Lipid Panel	Complete	UMinn		X	X	7,420 V3M=1603 V12M=1334 V24M=1203 V36M=1105 V48M=983 V60M=700 V72M=353 V84M=139	7,420 V3M=1603 V12M=1334 V24M=1203 V36M=1105 V48M=983 V60M=700 (2) V72M=353 V84M=139	Roche ModP (Dec 2009-2013); Roche Cobas 6000 (Jan 2014-present)	Parent	Started Dec 2009
Chemistry Panel	Complete	UMinn		X	X	7,420 V3M=1603 V12M=1334 V24M=1203 V36M=1105 V48M=983 V60M=700 V72M=353 V84M=139	7,420 V3M=1603 V12M=1334 V24M=1203 V36M=1105 V48M=983 V60M=700 (1) V72M=353 V84M=139	Roche ModP (Dec 2009-2013); Roche Cobas 6000 (Jan 2014-present)	Parent	Started Dec 2009
Cystatin C	Complete	UMinn		X	X	3,598 V3M=1486 V12M=1071 V24M=693 V36M=307 V48M=41		Siemens	Parent	Dec 2009-May 2014

ASSESS AKI Novel Biomarker Measurements - **Adults** 10/03/2019

Core Measurements	Status	Assay site	V0	V3M	Annually	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
Urine										
Albumin	Complete	UMinn		X	X	7,394 V3M=1603 V12M=1325 V24M=1189 V36M=1090 V48M=990 V60M=703 V72M=362 V84M=132	7,380 V3M=1603 (2) V12M=1325 (4) V24M=1189 (2) V36M=1090 **V48M=987** **V60M=692** V72M=362 V84M=132	Siemens ProSpec nephelometric	Parent	Started Dec 2009
Creatinine	Complete	UMinn		X	X	7,394 V3M=1603 V12M=1325 V24M=1189 V36M=1090 V48M=990 V60M=703 V72M=362 V84M=132	7,391 V3M=1603 **V12M=1323** V24M=1189 V36M=1090 V48M=990 **V60M=702** V72M=362 V84M=132	Roche ModP (Dec 2009-2013); Roche Cobas 6000 (Jan 2014-present)	Parent	Started Dec 2009
Protein	Complete	UMinn		X	X	7,394 V3M=1603 V12M=1325 V24M=1189 V36M=1090 V48M=990 V60M=703 V72M=362 V84M=132	7,391 V3M=1603 **V12M=1323** V24M=1189 V36M=1090 V48M=990 **V60M=702** V72M=362 V84M=132	Roche ModP (Dec 2009-2013); Roche Cobas 6000 (Jan 2014-present)	Parent	Started Dec 2009

ASSESS AKI Novel Biomarker Measurements - **Adults** 10/03/2019

Core Measurements	Status	Assay site	V0	V3M	Annually	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
Serum (+ V0 samples are plasma)										
Cystatin C (Re-measure of those measured using the Siemens reagent to avoid recalibration)	Complete	UMinn	X	X	X	5,055 V0=1539 (plasma) V3M=1432 (plasma) V12M=1052 (serum) V24M=689 (serum) V36M=302 (serum) V48M=41 (serum)	**5,219** **V0=1537** **V3M=1552** **V12M=1062** **V24M=704** **V36M=315** **V48M=49**	Roche Cobas 6000 (Gentian)	Parent	
Cystatin C	Complete	UMinn	X+	X	X	3,790 V3M=117 V12M=263 V24M=510 V36M=798 V48M=934 V60M=681 V72M=350 V84M=137	**3,774** **V3M=116** **V12M=254** **V24M=494** **V36M=784** V48M=934 **V60M=700** **V72M=353** **V84M=139**	Roche Cobas 6000 (Gentian)	Parent	May 2014-present

Cystatin C was measured using the Dade/Siemens reagent from the beginning of ASSESS testing through April 30, 2014. The Gentian cystatin C method was instituted for samples tested beginning on May 1, 2014 and later. There was drift in the calibration of the Dade/Siemens method noted by the DCCT/EDIC study JASN 2014; 25: 810-8. Ultimately, the decision was made to re-measure all ASSESS-AKI samples using the Gentian method to avoid the need to recalibrate results.

ASSESS AKI Novel Biomarker Measurements - **Adults** 10/03/2019

Novel Biomarker Measurements	Status - Planned/ In Progress	Assay site	V0	V3M	V12M	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
Urine										
Interleukin-18 (IL-18)	Complete	Cinn	X	X		1,732 V0=866 V3M=866	1,732 V0=866 V3M=866	ELISA	Parent	May 2013
Interleukin-18 (IL-18)	Complete	UVM	X	X	X	4,527 V0=1600 V3M=1602 V12M=1325	**4,515 V0=1596 V3M=1598 V12M=1321**	MSD	Parent	May 2017
Liver-type fatty acid binding protein (L-FABP)	Complete	Cinn	X	X		1,732 V0=866 V3M=866	1,732 V0=866 V3M=866	ELISA	Parent	June 2015
Neutrophil gelatinous-associated lipocalin (NGAL)	Complete	Cinn	X	X		1,732 V0=866 V3M=866	1,732 V0=866 V3M=866	ELISA	Parent	May 2013
Neutrophil gelatinous-associated lipocalin (NGAL)	Complete	UVM	X	X	X	4527 V0=1600 V3M=1602 V12M=1325	**4,515 V0=1596 V3M=1598 V12M=1321**	MSD	Parent	May 2017
Kidney injury molecule-1 (KIM-1)	Complete	Cinn	X	X		1,732 V0=866 V3M=866	1,732 V0=866 V3M=866	ELISA	Parent	May 2013
Kidney injury molecule-1 (KIM-1)	Complete	UVM	X	X	X	4527 V0=1600 V3M=1602 V12M=1325	**4,515 V0=1596 V3M=1598 V12M=1321**	MSD	Parent	May 2017
Discovery proteomics	Ongoing	Yale		X		68 matched pairs V3M=68		Mass Spec	Parent	Started Mar 2017
Osmolality	Complete	UMinn	X	X	X	4515 V0=1596 V3M=1598 V12M=1321	4515 V0=1596 V3M=1598 V12M=1321	Freezing point depression	Parent	June 2017

ASSESS AKI Novel Biomarker Measurements - **Adults** 10/03/2019

Novel Biomarker Measurements	Status - Planned/ In Progress	Assay site	V0	V3M	V12M	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
Urine * These measurements were made as part of the core protocol at subsequent visits										
Albumin	Complete	UMinn	X	*	*	V0=1596	V0=1596	Immunoturbidimetry	Parent	V0: June 2017
Creatinine	Complete	UMinn	X	*	*	V0=1596	V0=1596	Enzymatic	Parent	V0: June 2017
Protein	Complete	UMinn	X	*	*	V0=1596	V0=1596	Benzethonium chloride	Parent	V0: June 2017
Uromodulin	Ongoing	UVM	X	X	X	4527 V0=1600 V3M=1602 V12M=1325	**4,515** **V0=1596** **V3M=1598** **V12M=1321**	MSD	Ancillary (Parikh, Cantley)	May 2013
MCP-1	Complete	UVM	X	X	X	4527 V0=1600 V3M=1602 V12M=1325	**4,515** **V0=1596** **V3M=1598** **V12M=1321**	MSD	Ancillary (Parikh, Cantley)	May 2017
YKL-40	Complete	UVM	X	X	X	4527 V0=1600 V3M=1602 V12M=1325	**4,515** **V0=1596** **V3M=1598** **V12M=1321**	MSD	Ancillary (Parikh, Cantley)	May 2017
MMP-2, MMP-7 (instead of CTGF)	Complete	Yale		X	X	400 V3M=200 V12M=200	400 V3M=200 V12M=200	MSD	Ancillary (Mansour)	August 2017
MMP-2, MMP-7 (instead of CTGF)	In Progress	Hopkins	X	X	X	4,342 V0=1534 V3M=1535 V12M=1273		MSD	Ancillary (Mansour)	Jan 2020
PIIINP	In Progress	Hopkins	X	X	X	4,342 V0=1534 V3M=1535 V12M=1273		MSD	Ancillary (Mansour)	Jan 2020

ASSESS AKI Novel Biomarker Measurements - **Adults** 10/03/2019

Novel Biomarker Measurements	Status - Planned/ In Progress	Assay site	V0	V3M	V12M	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
Urine										
Discovery metabolomics	In Progress	UTXSA				80 SUBS (stored at -80C condition) 50 SUBS (stored at 25C prior to freezing at -80C)		Mass spectro scopy	Ancillary (Reeves)	Started April 2018
Idoxyl sulfate	In Progress	UW	X	X	X	4,306 V0=1527 V3M=1508 V12M=1271		HPLC/Mass Spec	Ancillary	2019
p-cresol sulfate	In Progress	UW	X	X	X	4,306 V0=1527 V3M=1508 V12M=1271		HPLC/Mass Spec	Ancillary	2019
hippurate	In Progress	UW	X	X	X	4,306 V0=1527 V3M=1508 V12M=1271		HPLC/Mass Spec	Ancillary	2019
Confirmatory Assays	In Progress	UW	X	X	X	4,306 V0=1527 V3M=1508 V12M=1271		Mass Spec or Immunoassay	Ancillary	2019

ASSESS AKI Novel Biomarker Measurements - **Adults** 10/03/2019

Novel Biomarker Measurements Planned/In Progress	Status	Assay site	V0	V3M	V12M	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
EDTA Plasma										
V-PLEX (10 plex) proinflammatory panel: IFN-g, IL-10, IL-12p70, IL-13, IL-1β, IL-2, IL-4, IL-6, IL-8, TNFα	Complete	UVM	X	X	X	4,494 V0=1583 V3M=1529 V12M=1306 76 duplicates V12M	4,494 V0=1583 V3M=1529 V12M=1306	MSD	Parent & ancillary (Liu -IL-6)	Part 1: August 2017 Part 2: March 2018
TNFa RI/RII	Complete	UVM	X	X	X	4,494 V0=1583 V3M=1529 V12M=1306 76 duplicates V12M	4,494 V0=1583 V3M=1529 V12M=1306	MSD	Parent	Part 1: August 2017 Part 2: March 2018
Idoxyl sulfate	In Progress	UW	X	X	X	4,306 V0=1527 V3M=1508 V12M=1271		HPLC	Parent	2019
p-cresol sulfate	In Progress	UW	X	X	X	4,306 V0=1527 V3M=1508 V12M=1271		HPLC	Parent	2019
hippurate	In Progress	UW	X	X	X	4,306 V0=1527 V3M=1508 V12M=1271		HPLC	Parent	2019
Intact parathyroid hormone (PTH) (pg/mL)	Complete	UMinn	X	X		3236 V0=1537 + 101 replicate V3M=1548 + 50 replicate	**3,084 V0M=1536** V3M=1548	Cobas (clinical analyzer)	Ancillary (Liu)	April 2016

ASSESS AKI Novel Biomarker Measurements - **Adults** 10/03/2019

Novel Biomarker Measurements Planned/In Progress	Status	Assay site	V0	V3M	V12M	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
EDTA Plasma										
Phosphorus (mg/dL)	Complete	UMinn	X	X		3236 V0=1537 + 101 replicate V3M=1548 + 50 replicate	**3,085 V0M=1537** V3M=1548	Cobas	Ancillary (Liu)	April 2016
C reactive protein (CRP) (mg/L)	Complete	UMinn	X	X		3236 V0=1537 + 101 replicate V3M=1548 + 50 replicate	**3,083 V0M=1535** V3M=1548	Cobas	Ancillary (Liu)	April 2016
Fibroblast growth factor 23 (FGF 23) (pg/mL)	Complete	UMinn	X	X		3236 V0=1537 + 101 replicate V3M=1548 + 50 replicate	**3,086 V0M=1538** V3M=1548	Kainos ELISA	Ancillary (Liu)	April 2016
Vitamin D metabolites	In Progress	UW	X	X				Mass Spec	Ancillary (Liu)	
Ang-1, Ang -2	Complete	Yale		X	X	400 V3M=200 V12M=200	400 V3M=200 V12M=200	MSD	Ancillary (Mansour)	August 2017
TGF-B	Complete	Yale		X	X	400 V3M=200 V12M=200	400 V3M=200 V12M=200	MSD	Ancillary (Mansour)	August 2017
Angiogenesis Panel: VEGF, PIGF, FLT1, bFGF, Tie-2	Complete	Yale		X	X	400 V3M=200 V12M=200	400 V3M=200 V12M=200	MSD	Ancillary (Mansour)	August 2017
Ang-1, Ang -2	Complete	Hopkins	X	X	X	4,294 V0=1526 V3M=1504 V12M=1268	4,294 V0=1526 V3M=1504 V12M=1268	MSD	Ancillary (Mansour)	August 2019

ASSESS AKI Novel Biomarker Measurements - **Adults** 10/03/2019

Novel Biomarker Measurements Planned/In Progress	Status	Assay site	V0	V3M	V12M	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
EDTA Plasma										
Angiogenesis Panel: VEGF, PIGF, FLT1, bFGF, Tie-2	Complete	Hopkins	X	X	X	4,294 V0=1526 V3M=1504 V12M=1268	4,294 V0=1526 V3M=1504 V12M=1268	MSD	Ancillary (Mansour)	July 2019
IL-17A	In Progress	IU		X	X	V3M=1504 V12M=1268		ELISA	Ancillary (Basile)	2019
IL17F	In Progress	IU		X	X	V3M=1504 V12M=1268		ELISA	Ancillary (Basile)	2019
IL23	In Progress	IU		X	X	V3M=1504 V12M=1268		ELISA	Ancillary (Basile)	2019

IU= Indiana University School of Medicine

Novel Biomarker Measurements Planned/In Progress	Status	Assay site	V0	V3M	V12M	V24M	V36M	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
EDTA Plasma												
sTNFR, KIM-1	In Progress	MSSM	X	X	X	X	X				Ancillary (Coca)	2019

MSSM=Mount Sinai School of Medicine

Appendix II. ASSESS AKI Novel Biomarker Measurements – Pediatrics

ASSESS AKI Novel Biomarker Measurements - Pediatrics 07/09/2019

Pediatric Core Measurements	Status	Assay site	V0	V3M	Annually	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
Urine										
Albumin	Complete	UMinn		X	X	V3M=121 V12M=116 V24M=112 V36M=106 V48M=104 V60M=93 V72M=64 V84M=30	**V3M=120 (1)** V12M=116 (2) V24M=112 (2) V36M=106 (1) **V48M=103 (1)** V60M=93 V72M=64 V84M=30	Siemens ProSpec nephelometric	Parent	Started Dec 2009
Creatinine	Complete	UMinn		X	X	V3M=121 V12M=116 V24M=112 V36M=106 V48M=104 V60M=93 V72M=64 V84M=30	**V3M=120** V12M=116 V24M=112 V36M=106 **V48M=103** V60M=93 V72M=64 V84M=30	Roche ModP (Dec 2009-2013); Roche Cobas 6000 (Jan 2014-present)	Parent	Started Dec 2009
Protein	Complete	UMinn		X	X	V3M=121 V12M=116 V24M=112 V36M=106 V48M=104 V60M=93 V72M=64 V84M=30	**V3M=120** V12M=116 V24M=112 V36M=106 **V48M=103** V60M=93 V72M=64 V84M=30	Roche ModP (Dec 2009-2013); Roche Cobas 6000 (Jan 2014-present)	Parent	Started Dec 2009
Plasma										
Creatinine	Complete	UMinn		X	X	V3M=115 V12M=112 V24M=105 V36M=100 V48M=98 V60M=81 V72M=52 V84M=26	**V3M=113** V12M=112 V24M=105 V36M=100 V48M=98 (2) V60M=81 (2) V72M=52 V84M=26	Roche ModP (Dec 2009-2013); Roche Cobas 6000 (Jan 2014-present)	Parent	Started Dec 2009

ASSESS AKI Novel Biomarker Measurements - Pediatrics 07/09/2019

Pediatric Core Measurements	Status	Assay site	V0	V3M	Annually	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
Plasma										
Cystatin C+	Complete	UMinn		X	X	V3M=115 V12M=112 V24M=93 V36M=45 V48M=11		Siemens	Parent	Dec 2009-May 2014
Cystatin C (re-measure)	Complete	UMinn		X	X	V12M=4 V24M=35 V36M=25 V48M=8	V12M=4 **V24M=37** **V36M=28** **V48M=14**			
Cystatin C+	Complete	UMinn		X	X	V24M=12 V36M=55 V48M=87 V60M=81 V72M=52 V84M=26	**V24M=10** **V36M=52** **V48M=82** V60M=81 V72M=52 V84M=26	Roche Cobas 6000 (Gentian)	Parent	May 2014-present

+Cystatin C was measured using the Dade/Siemens reagent from the beginning of ASSESS testing through April 30, 2014. The Gentian cystatin C method was instituted for samples tested beginning on May 1, 2014 and later. There was drift in the calibration of the Dade/Siemens method noted by the DCCT/EDIC study JASN 2014; 25: 810-8. Ultimately, the decision was made to re-measure all ASSESS-AKI samples using the Gentian method to avoid the need to recalibrate results.

ASSESS AKI Novel Biomarker Measurements - Pediatrics 07/09/2019

Peds Novel Biomarker Measurements	Status	Assay site	V0	V3 M	V12 M	V24 M	V36M - V48M	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
Urine												
Interleukin-18 (IL-18)	Complete	PATR	X	X	X	X		V0=118 V3M=118 V12M=115 V24M=112	V0=118 V3M=118 V12M=115 V24M=112	MSD	Parent	June 2015
Liver-type fatty acid binding protein (L-FABP)	Complete	PATR	X	X	X	X		V0=118 V3M=118 V12M=115 V24M=112	V0=118 V3M=118 V12M=115 V24M=112	ELISA	Parent	June 2015
Neutrophil gelatinase-associated lipocalin (NGAL)	Complete	PATR	X	X	X	X		V0=118 V3M=118 V12M=115 V24M=112	V0=118 V3M=118 V12M=115 V24M=112	ELISA	Parent	June 2015
Kidney injury molecule-1 (KIM-1)	Complete	PATR	X	X	X	X		V0=118 V3M=118 V12M=115 V24M=112	V0=118 V3M=118 V12M=115 V24M=112	ELISA	Parent	June 2015
Uromodulin	Complete	PATR	X	X	X	X		V0=118 V3M=118 V12M=115 V24M=112	V0=118 V3M=118 V12M=115 V24M=112	MSD	Ancillary (Parikh, Cantley)	June 2015
MCP-1	Complete	PATR	X	X	X	X		V0=113 V3M=100 V12M=101 V24M=94	V0=113 V3M=100 V12M=101 **V24M=95**		Ancillary (Greenberg)	
YKL-40	Complete	PATR	X	X	X	X		V0=113 V3M=100 V12M=101 V24M=94	V0=113 V3M=100 V12M=101 **V24M=95**		Ancillary (Greenberg)	

ASSESS AKI Novel Biomarker Measurements - Pediatrics 07/09/2019

Peds Novel Biomarker Measurements	Status	Assay site	V0	V3 M	V12 M	V24 M	V36M - V48M	Samples Pulled	Samples Analyzed	Bioassay platform	Parent or ancillary	Time frame
Urine												
PIIINP	In Progress	PATR	X	X	X	X		V0=113 V3M=100 V12M=101 V24M=94			Ancillary (Greenberg)	
Osmolality	Complete	UMinn	X	X	X			V0=69 V3M=87 V12M=84	V0=69 V3M=87 V12M=84	Freezing point depression	Parent	July 2017
Albumin	Complete	PATR	X	*	*			V0=118 V3M=118 V12M=115 V24M=112	V0=118 V3M=118 V12M=115 V24M=112	Immuno-turbidimetry	Parent	June 2015
Creatinine	Complete	PATR	X	*	*			V0=118 V3M=118 V12M=115 V24M=112	V0=118 V3M=118 V12M=115 V24M=112	Enzymatic	Parent	June 2015
Protein	Complete	UMinn	X	*	*			V0=69	V0=69	Benzethonium chloride	Parent	July 2017

* These measurements were made as part of the core protocol at subsequent visits

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ASsessment,
Serial Evaluation, and
Subsequent Sequelae in AKI
NIH/NIDDK

Event Adjudication Manual of Procedures

(EA MOP)

Version:

March 2020

Contents

1 INTRODUCTION

A central goal of the Assessment, Serial Evaluation, and Subsequent Sequelae in AKI (ASSESS-AKI) Study is to explore the association between an episode of acute kidney injury in the hospital and the development and/or progression of chronic kidney disease and vascular events. Additionally, the ASSESS-AKI Study will explore factors that may be associated with recurrent episodes of AKI. With regards to clinical outcome events, the ASSESS-AKI Study will rely primarily on participant self-report and subsequent targeted review of relevant medical records to determine whether study-related outcome events occur.

The present document describes the overall approach and methods to identify, adjudicate, and classify the occurrence of study-related outcome events.

1.A *Process of Identifying Potential Outcome Events*

The general approach will be to obtain self-reported and/or database information on potential study outcome events and subsequently obtain information on qualifying diagnostic and/or procedure codes at each Clinical Research Center (CRC), which will facilitate review of relevant medical records to abstract and to adjudicate. The event adjudication process begins at the six-month phone interview (V6M) and continues for all subsequent in-person visits and interim phone interviews; it does not include the events that occur between Visit 0 and Visit 3M. During the in-person visits and phone interviews, participants are asked if they have experienced any cardiovascular events, peripheral vascular events, cerebrovascular events, renal events, procedures and/or other medical events since their last study contact. The answers are recorded on the Adult/Pediatric Medical Events Questionnaire (P1/P2_EVENTS) form.

If a potential outcome event has occurred, the CRCs complete and data enter the appropriate data collection forms. Detailed instructions for the event data collection forms completed by the Research Coordinators are in Section 2 of the Protocol-Specific MOP, and those completed by the reviewers are available in Section 6 of the Event Adjudication MOP. Instructions to complete the Event Adjudication Checklist (EA_CHK) are in Section 3.C. of the Event Adjudication MOP. Medical events with qualifying diagnoses and procedural codes will prompt medical record review. Research Coordinators at each CRC will obtain relevant medical records and applicable reports (depending on the outcome event), remove the Personally Identifiable Information (PII) from the records and reports (See Section 3.C.2.), and along with the case report forms (CRFs) create PDFs using Adobe Acrobat Professional 9.0 or later, and place the de-identified medical records as PDFs on a DVD to be transferred to the Data Coordinating Center (DCC).

1.B *Process of Adjudicating Events*

The initial process for adjudicating events will be a validation effort focused on the accuracy and reliability of local adjudication. After the CRC has two “certified” reviewers, who have passed the adjudication training requirements, events will be locally adjudicated at that CRC; two reviewers who are not certified should not adjudicate the same event. The remaining “uncertified” reviewers must adjudicate events with a “certified” reviewer until they become certified. Assuming that the quality threshold is met at a CRC, the DCC will randomly select 10% of events from each local CRC to undergo central adjudication on a quarterly basis or after a certain number of accumulated events to monitor the quality of the local review process on an on-going basis.

For central adjudication, reviewers from CRCs other than the CRC where the event occurred adjudicate the events that occur during a single hospitalization. Each reviewer enters a decision and any optional comments into the corresponding module in the data management system (DMS).

The DCC compares the reviewers' decisions and follows a process to reach consensus between reviewers. After an event has been adjudicated and consensus has been reached, the information is verified by the DCC in the final dataset of the ASSESS-AKI Study.

1.C *Event Adjudication Committee (EAC)*

The purpose of the Event Adjudication Committee (EAC) is to centrally and locally adjudicate potential outcomes events based on a review of relevant medical records. The EAC is comprised of physician investigators from each of the CRCs. Adult physician reviewers will adjudicate adult events and pediatric physician reviewers will adjudicate pediatric events. A neurologist will serve as a consultant to local adjudicators in the case of cerebrovascular events when there is uncertainty regarding classification of the event. A cardiologist will serve as a consultant when local adjudicators are unable to reach consensus on cardiac events.

2 OUTCOMES

2.A *Renal Outcomes*

2.A.1 Incident Chronic Kidney Disease (CKD)

Among adult participants without pre-existing CKD at the index hospitalization, we will examine time to development of incident CKD with significant loss of renal function defined as experiencing at least a 25% reduction in level of eGFR compared with baseline (i.e., before the index hospitalization) AND achieving CKD Stage 3 or worse during follow-up. This outcome is only based on ASSESS-collected laboratory findings and will not require physician adjudication.

In children, incident CKD will only be evaluated at the V12M onward in participants who had their index surgery at age less than nine months old. In other pediatric participants, incident CKD will be evaluated at all visits. Incident CKD will be defined as having a GFR<90ml/min/1.73m^2. In children who had their index surgery at age one year or later, change in GFR from baseline to the date of visit/ascertainment will be documented and compared between AKI and non-AKI pediatric participants. For all pediatric participants (including those having their index surgery at age less than one year old), change in GFR percentile will be described and compared between AKI and non-AKI pediatric participants.

2.A.2 Progression of CKD

Among adult participants with pre-existing CKD at the index hospitalization (defined as a baseline eGFR <60 ml/min/1.73m^2), we will examine time to progression of CKD, defined as experiencing at least a 50% reduction in level of eGFR compared with baseline kidney function OR progressing to CKD Stage 5. This outcome is only based on ASSESS-collected laboratory findings and will not require physician adjudication.

In children, the change in GFR and in GFR percentile over time will be described and compared between AKI and non-AKI pediatric participants, as described in 2.A.1.

2.A.3 Development of End-Stage Renal Disease (ESRD)

Development of ESRD will be defined as meeting any of the following criteria: (1) receipt of any outpatient dialysis after V3M; (2) death while receiving inpatient dialysis lasting ≥28 days; and/or (3) receipt of a kidney transplant. This outcome will be assessed on an interval basis every six months by direct questioning of the participant or review of medical records for hospitalization. Death while receiving new (i.e., in the absence of prior chronic outpatient dialysis) inpatient dialysis lasting <28 days or receipt of new inpatient dialysis lasting <28 days and being discharged from the hospital off dialysis will be considered dialysis-requiring AKI.

Example: Participant is discharged (at any day of dialysis) and receives outpatient Hemodialysis; ESRD is included in the diagnoses. At the next visit (6-month or yearly), if the participant is still on dialysis, then ESRD is confirmed; if off dialysis, we obtain the last date of dialysis and participant is checked as "recovered renal function." These latter cases are subsequently switched from ESRD to AKI.

2.A.4 Incident or Recurrent Episodes of AKI

We will attempt to ascertain incident and recurrent episodes of AKI using available laboratory results obtained during hospitalizations occurring throughout the follow-up period. Episodes of AKI will use the

same criteria as for entry into ASSESS-AKI (i.e., change in serum creatinine concentration using the peak inpatient value compared with the most recent pre-admission ASSESS-AKI Study serum creatinine result), although we will also potentially consider other definitions of AKI. For cases of laboratory-defined AKI, there will be additional information obtained from the medical records and reviewed by physician reviewers. However, this will not require physician adjudication.

2.B *Cardiovascular Outcomes*

2.B.1 Coronary Heart Disease

Standard definitions will be used to classify a coronary heart disease event.

- Acute coronary syndrome will be based on documented evidence of ischemic symptoms plus: transient ST-T wave changes and no elevated cardiac enzymes such as cardiac troponin (i.e., unstable angina); elevated cardiac enzymes without ST-elevation on electrocardiogram (ECG) (i.e., non-ST-elevation myocardial infarction); or elevated cardiac enzymes and ST-elevation or Q waves on ECG (i.e., ST-elevation myocardial infarction). Refer to the Reference Cards for the ICD-9/ICD-10 codes. This outcome will not be evaluated in the pediatric participants.

- Sudden cardiac death will be obtained by mortality files and subject proxy contacts. It will be defined as either an unwitnessed death without another obvious cause or death occurring within one hour of the onset of ischemic symptoms per a proxy.

- Heart failure will be based on hospitalizations for a clinical heart failure syndrome using primary discharge ICD-9 codes or corresponding ICD-10 codes and confirmed based primarily on Framingham Heart Study clinical criteria ascertained from medical records. Refer to the Reference Cards for the ICD-9/ICD10 codes. We will not require evidence of systolic dysfunction (e.g., left ventricular ejection fraction <40%) or diastolic dysfunction on echocardiography given that we are primarily interested in clinical heart failure and current evidence suggests that more than half of adults with heart failure have preserved left ventricular systolic function.

- Coronary artery revascularization will include either percutaneous coronary intervention with or without intracoronary stenting or coronary artery bypass surgery of one or more coronary blood vessels. Refer to the Reference Cards for the ICD-9/ICD-10 codes. This outcome event will not be centrally adjudicated as the corresponding procedure codes have high sensitivity and specificity. This outcome will not be evaluated in the pediatric participants.

- Silent myocardial infarction will be defined as new, pathologic Q waves on serial ECGs among the subgroup of enrolled adult participants with the event date assigned as the mid-point between the relevant annual visits. This outcome event will be defined based on the review by the ECG Reading Center. This outcome will not be evaluated in the pediatric participants.

2.B.2 Cerebrovascular Disease Outcomes

The pertinent cerebrovascular disease outcomes include ischemic stroke, intracranial hemorrhage, and carotid endarterectomy.

- Ischemic stroke will be defined as acute development of a neurological deficit fitting a vascular distribution, lasting ≥24 hours, and no other evident etiology such as intracranial hemorrhage, vasculitis, tumor, or trauma. This definition has been validated in other epidemiological studies. Refer to the Reference Cards for the ICD-9/ICD-10 codes . Supporting brain imaging (e.g., CT or MRI) will be sought but will not be required for diagnosis.

- Intracranial hemorrhage will require validation by brain imaging or pathologic evidence and should have a documented history consistent with a stroke syndrome, diminished consciousness, or headache. Refer to the Reference Cards for the ICD-9/ICD-10 codes.

- Carotid endarterectomy will include both surgical endarterectomy and balloon angioplasty with or without carotid stent placement. Refer to the Reference Cards for the ICD-9/CPT codes and ICD-10/CCI codes. This outcome event will not be centrally adjudicated as the corresponding procedure codes have high sensitivity and specificity.

2.B.3 Peripheral Arterial Disease Outcomes

Pertinent peripheral arterial disease outcomes include lower extremity arterial revascularization or amputation for refractory ischemia as well as aortic aneurysm repair.

- Lower extremity revascularization will include both percutaneous peripheral artery angioplasty and surgical arterial bypass procedures. Lower extremity amputation will include procedures performed for refractory ischemia. Refer to the Reference Cards for the ICD-9/CPT codes and ICD-10/CCI codes. This outcome event will not be centrally adjudicated as the corresponding procedure codes have high sensitivity and specificity.

- Thoracic or abdominal aortic aneurysm repair (using percutaneous or surgical procedures) based on corresponding ICD-9/ICD10 procedure codes and as needed, relevant CPT/CCI procedures codes. Refer to the Reference Cards for the ICD-9/CPT codes and ICD-10/CCI codes. The outcome event will not be centrally adjudicated as the corresponding procedure codes have high sensitivity and specificity.

3 EVENT INVESTIGATION

3.A *Clinical Research Center (CRC) Responsibilities*

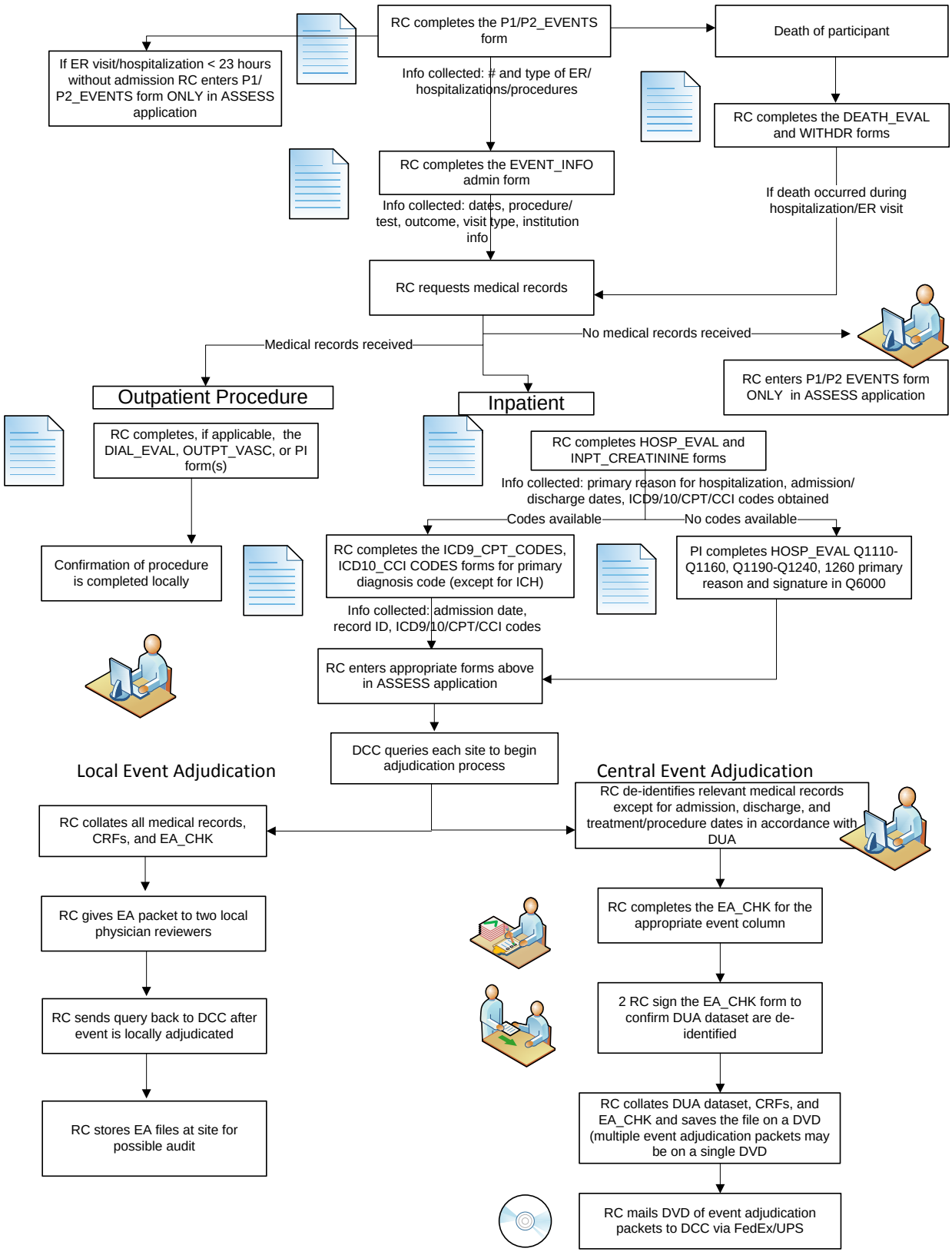
The event investigation process begins at the CRC. The specific responsibilities for the CRC include:

- Maintaining up-to-date medical record release and HIPAA authorization forms for each participant.
  - FOR US SITES: Complete the NIH Human Subjects Training On-Line Course

    (http://phrp.nihtraining.com) and/or the Collaborative Institutional Training Initiative (CITI – http://www.citiprogram.org/default.asp?language=english) as required by the specific site
  - FOR MONTREAL SITE: The MCH requires the following certification in clinical research: (http://ethique.msss.gouv.qc.ca/didacticiel/index.php?lang=en)
  - FOR ONTARIO SITE: Ontario requires Tri-Counsel Policy Statement: Ethical Conduct for Research Involving Humans (http://pre.ethics.gc.ca/english/tutorial/)
- Administering the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENT) to ASSESS-AKI Study participants at least every six months and entering it into the DMS.
- Entering all completed data collection forms into the DMS.
- Conducting an event investigation for each hospitalization (lasting >23 hours), ER visit (lasting >23 hours), and/or outpatient test/procedure beginning at the six-month visit (V6M).
- Creating PDFs using Adobe Acrobat Professional 9.0 or later of relevant de-identified medical records and forms.
- Sending the DVD via overnight or two-day mail service with tracking capabilities to the DCC.
- Identifying additional events that were not reported by the participant and are discovered while searching for a specific potential event.

3.B *Event Investigation Procedures*

Phase I of the Event Investigation: CRC Responsibilities is diagrammed in more detail below.



Detailed instructions for completing the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS), Event Information Sheet (EVENT_INFO), Hospital/ER Record Evaluation (HOSP_EVAL), and Inpatient Creatinine (INPT_CREATININE) forms are in the Protocol–Specific MOP, Sections 2.2.2/2.3.10, 2.4.5., 2.1.16, and 2.1.19.

3.B.1 Local Event Adjudication

The **local event adjudication** procedures for completing an event investigation at a CRC are described below.

1. Complete the P1/P2_EVENTS form during the in-person visit or phone interview. Complete the EVENT_INFO form for every potential event recorded.

    a. Prepare the relevant data collection forms based on responses on the P1/P2_EVENTS form.

    b. If the P1/P2_EVENTS form indicates that the participant has died outside of the hospital, complete the Death Evaluation (DEATH_EVAL) and Withdrawal (WITHDR) forms. If the P1/P2_EVENTS form indicates that the participant has died during a hospitalization/ER visit, complete the Death Evaluation (DEATH_EVAL), Withdrawal (WITHDR), and if medical records are available, the Hospital/ER Record Evaluation (HOSP_EVAL) and the Inpatient Creatinine (INPT_CREATININE) forms.

    c. Complete an EVENT_INFO form for every event recorded in Questions 1230/1130, 1290, 1350/1300, or 1390/1340 of the P1/P2_EVENTS form.

    d. Request relevant medical records from the treating facility.

    e. If no medical records are received despite multiple attempts to obtain them (including written and telephone requests) over 90 days, enter the P1/P2_EVENTS form. Continue to try to obtain medical records for six months.

2. If medical records are received and it is one of the specified outpatient procedures:

    a. Complete the Outpatient Dialysis Evaluation form (DIAL_EVAL), Outpatient Vascular Procedure Evaluation form (OUTPT_VASC), or Procedure Investigation (PI) form(s).

    b. Confirmation of the outpatient procedure(s) is completed locally.

3. If medical records are received and it is an inpatient event, complete the Hospital/ER Record Evaluation (HOSP_EVAL) and Inpatient Creatinine (INPT_CREATININE) forms.

    a. For the situation when medical records are available for an event, but it is impossible to obtain the administrative diagnostic and/or procedure codes, the Principal Investigator at the respective CRC will complete an assessment. The Principal Investigator completes Q1110-1160, Q1190-1240, and Q1260 of the HOSP_EVAL and records the primary discharge diagnosis and his/her signature in Q6000. Only those events listed as Q1110-1160 and Q1190-1240 marked 'Yes' will initiate an event adjudication query; those marked 'Unknown' will not initiate a query. Refer to Section 2.1.16 in the Protocol-Specific MOP for details when a HOSP_EVAL is not completed.

b. If codes are available, complete the ICD9/CPT Administrative Codes Sheet (ICD9_CPT_CODES) or ICD10/CCI Administrative Codes Sheets (ICD10_CCI_CODES) for every hospitalization/ER visit recorded in Questions 1230/1130, 1290, 1350/1300, and 1390/1340 of the P1/P2_EVENTS. ASSESS-AKI diagnosis codes in the primary position should be recorded except with intracranial hemorrhage, which includes primary and secondary position.

4. Enter all completed data collection forms into the DMS.

5. DCC queries each CRC to begin the adjudication process. Query is assigned a unique group number through the database, which becomes the EA tracking number.

6. To search for queries-related events that need to be adjudicated, click on the 'F' button next to the Form Name field. This will open another screen, then click on the View Misc Forms button, and select EA from the list and click 'OK'. When you click Execute Query, you will see a list of participants that need to have events investigated.

7. Complete the Event Adjudication Checklist (EA_CHK) (see Section 3.C.) for the appropriate event column. PII does not need to be redacted for local adjudication.

8. Collate all relevant medical records, case report forms, applicable reports, and EA_CHK.

9. Give the EA packet to a local reviewer.

10. Set query to DCC status.

11. Store the EA files securely at the CRC for possible future audit and/or central adjudication.

3.B.2 Central Event Adjudication

The central event adjudication procedures for completing an event investigation at a CRC are described below.

1. Follow steps 1-10 above related to local event adjudication.

2. Remove the Personally Identifiable Information (PII) from the relevant medical records except dates of services (for the purposes of accurately identifying study visits, exposures, and clinical events of interest such as, but not limited to, admission, discharge, and treatment/procedure dates) in accordance with Data Use Agreement (DUA) to create the DUA dataset using Adobe Acrobat Professional (version 9.0 or later) for each event. Blacken the Participant ID on the data collection forms; do not blacken the protocol and site number.

3. Complete the Event Adjudication Checklist (EA_CHK) (see section 3.C.) for the appropriate event column.

4. Two ASSESS-AKI study personnel at the CRC must review the DUA dataset for PII and confirm that all relevant PII has been removed by signing and dating the EA_CHK. Make sure you are using the most recent version of the EA_CHK.

5. Create PDFs using Adobe Acrobat Professional 9.0 or later of the DUA dataset and data collection forms. Blacken out the Participant ID in the header of the pdfs of the EA_CHK and data collection forms saved to the DVD. Do not blacken the protocol and site. The reviewer needs these to complete the fillable forms.

6. Collate the DUA dataset to be saved to the DVD in this order 1) EA_CHK, 2) follow the order listed in the columns on the EA_CHK, and 3) data collection forms. Save the file using the group number from the query which is the EA tracking number as the filename. Each file must be less than 7.5 MB (or <7,500 KB) to be able to post to the website so you may need to create (EA number)_Part 1, (EA_number)_Part 2, etc.

7. Multiple event adjudication packets may be saved on one DVD. List the EA tracking number(s) on the outside of the DVD.

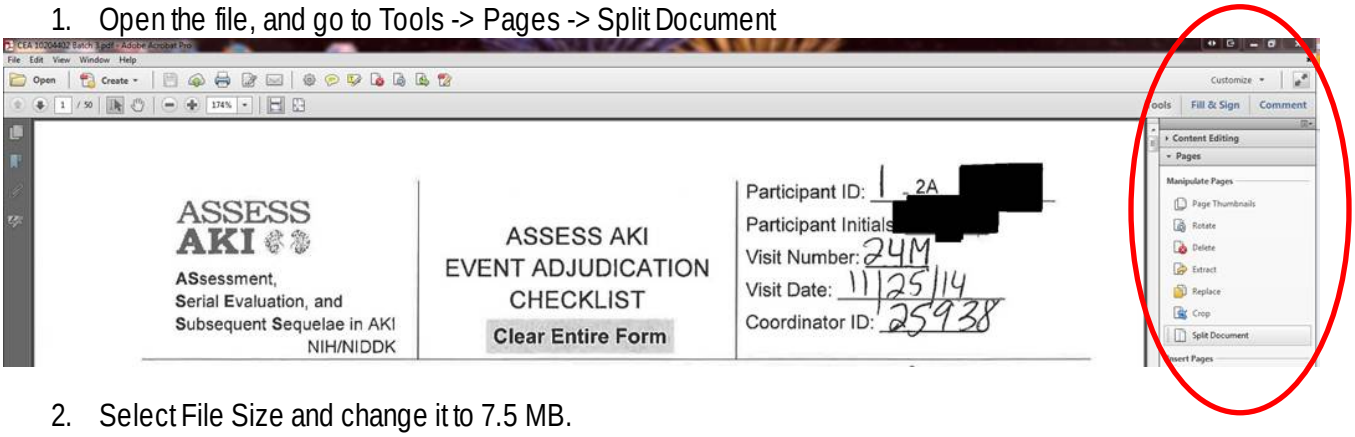
8. Set query to DCC status with the status that the DVD was sent along with the tracking number.

9. Send DVDs and a hardcopy of the EA_CHK <u>without</u> blackening the Participant ID to the DCC via overnight or two-day mail service with tracking capabilities with the weekly form shipments. Include the overnight or two-day mail service tracking number in the query response. DVDs can only be sent to the DCC if there is a signed DUA between the institution of the CRC and The Pennsylvania State University (PSU).

3.B.3 <u>Instructions for creating a split .pdf can be found here:</u>

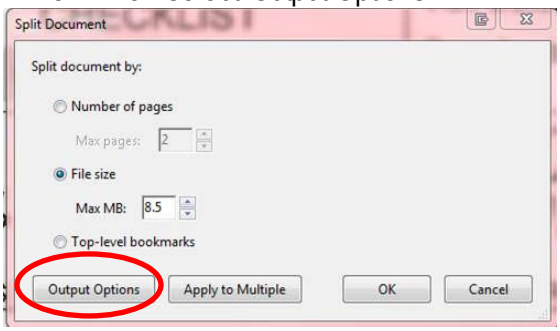
Adobe Acrobat Pro users:

1. Open the file, and go to Tools -> Pages -> Split Document

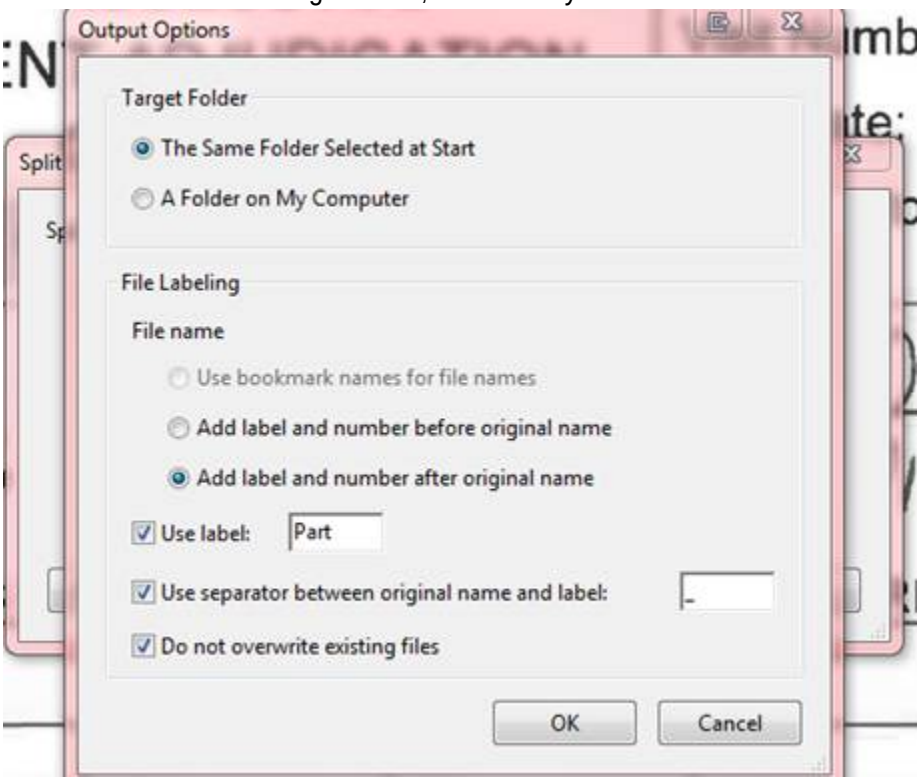


2. Select File Size and change it to 7.5 MB.

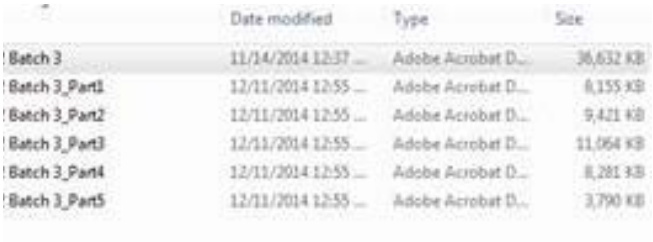
3. Then select 'Output Options'



4. In the File Labeling Section, make sure your screen looks like this:



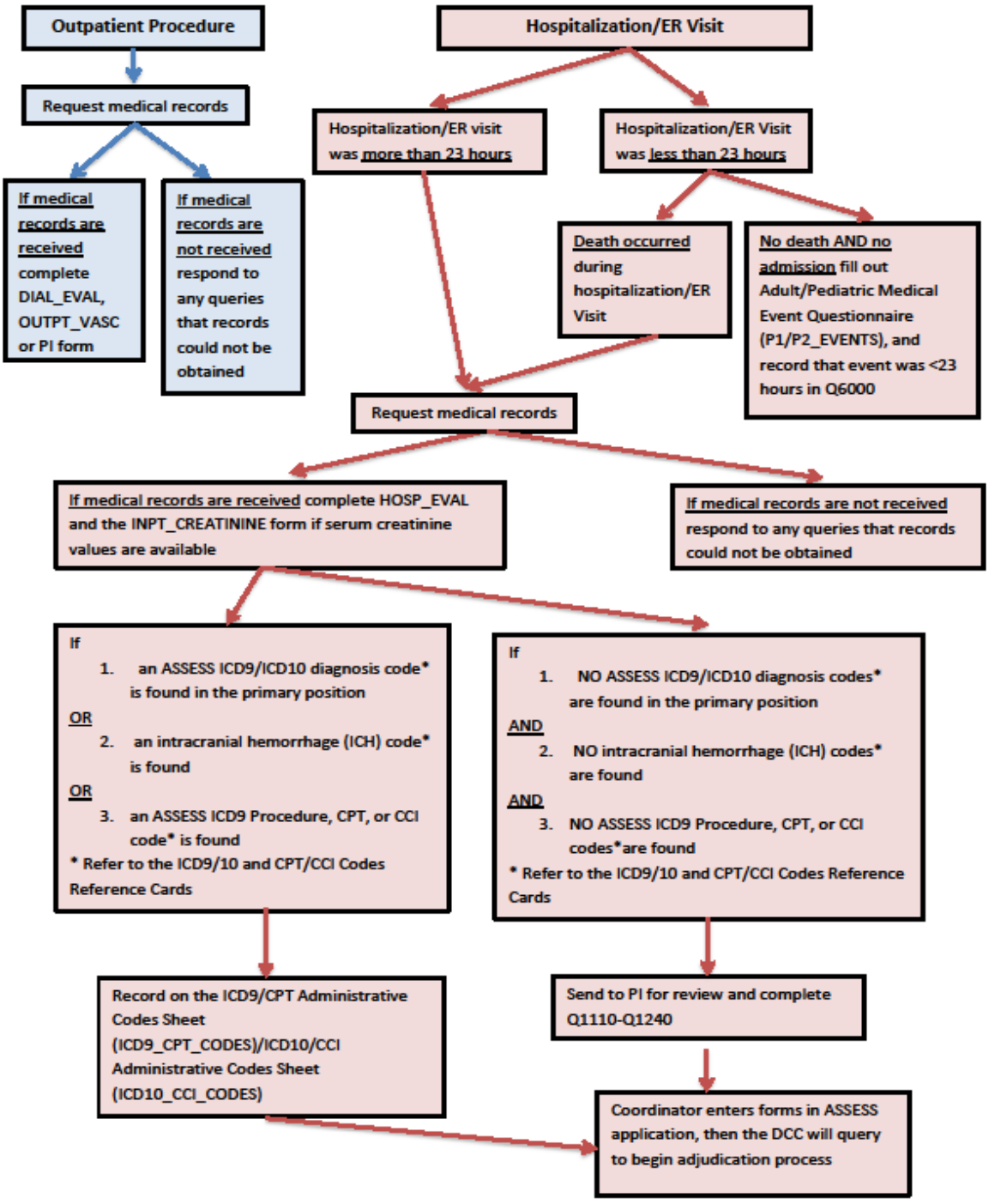
5. Then your original file and the new files will be in the same location:



Adobe Reader users:

1. Since Reader users do not have access to the split document feature, the simplest method is to only scan up to 10 documents in a .pdf. You will also not have the option to delete files, as with Adobe Acrobat Pro, so it would be easier to create the files smaller from the beginning.

3.B.4 Summary of Event Adjudication Steps for Coordinator Reference



3.C *Event Adjudication Checklist (EA_CHK)*

Purpose: To provide the Research Coordinator with a checklist of all the information needed to be extracted from the medical records for a given type of event.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: When completing the Event Adjudication packet.

Form Instructions:

This form serves as a guide to the Research Coordinator and should be sent to the DCC, along with the Event Adjudication packet.

A separate EA_CHK should be completed for each hospitalization, outpatient test, and/or outpatient procedure. For each hospitalization, outpatient test and/or outpatient procedure, indicate whether or not the specified documentation was found in the medical records.

Complete the Visit Date as the current date the Event Adjudication Checklist (EA_CHK) form is completed.

Note: This may not necessarily be the date the hospitalization(s) occurred.

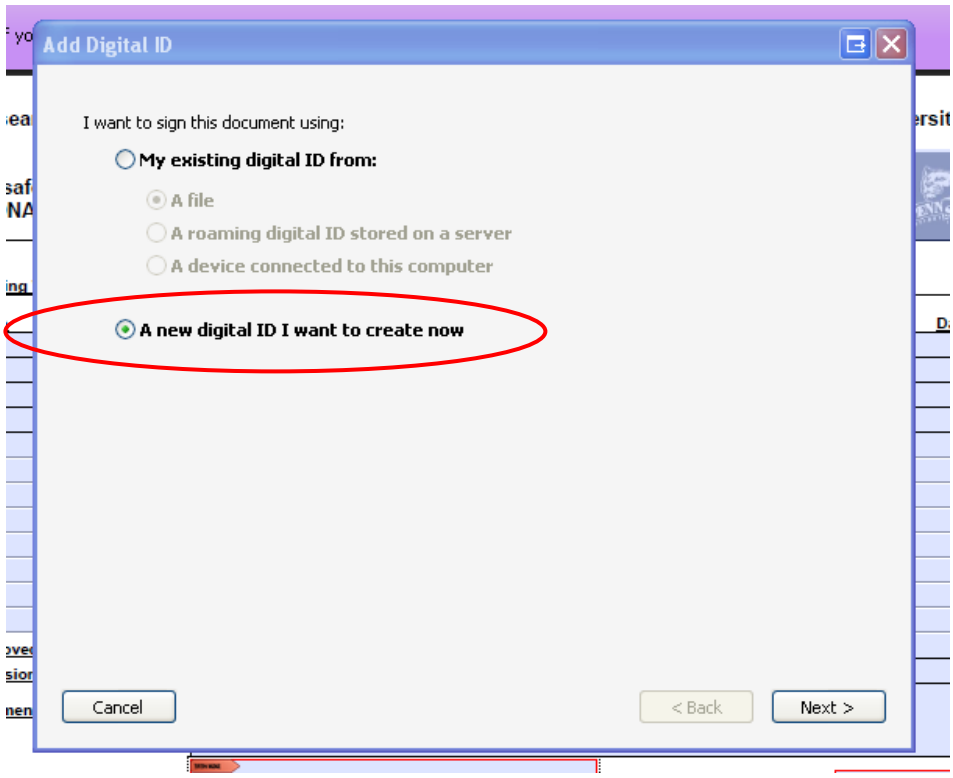
Admission Date. Record the admission date of the hospitalization based on the medical records for the event being adjudicated.

Discharge Date. Record the discharge date of the hospitalization based on the medical records for the event being adjudicated.

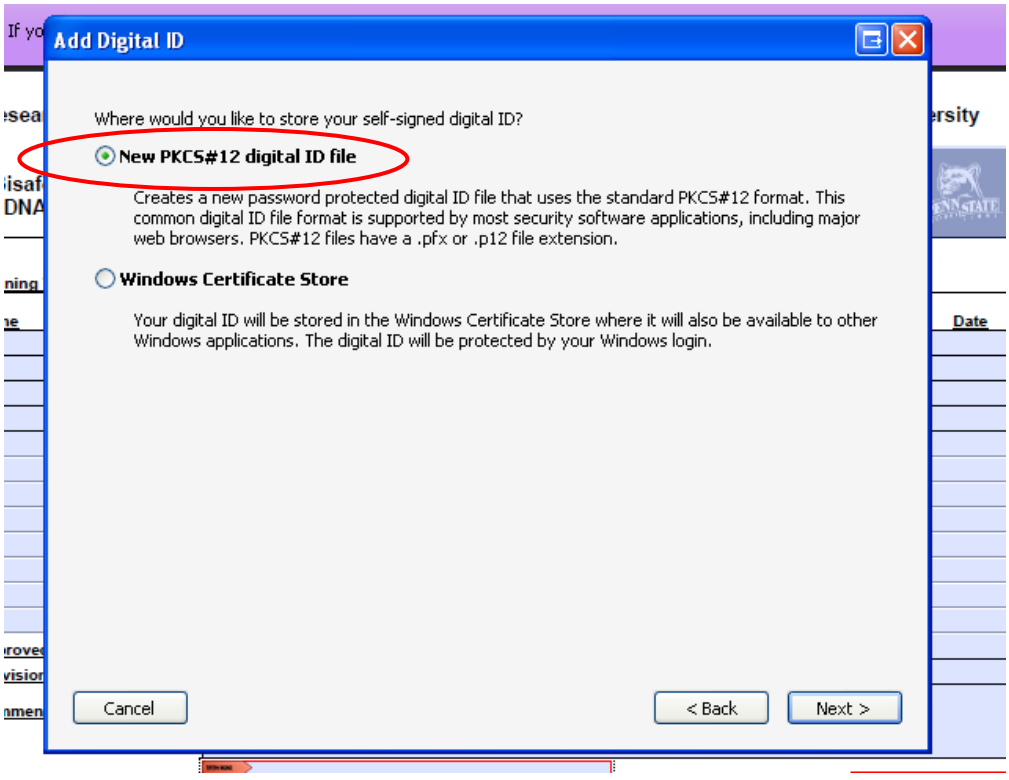
For central event adjudication, two different Research Coordinators must review the packet and sign the EA_CHK to confirm that the packet does not contain any PII elements in the contained records being transferred except dates of services (for the purposes of accurately identifying study visits, exposures, and clinical events of interest such as, but not limited to, admission, discharge, and treatment/procedure dates) as described in the Data Use Agreement (DUA) between the CRC and the PSU. PII does not need to be redacted for local adjudication. This form can be signed manually and added to the front of the packet or signed electronically.

To sign the form electronically:

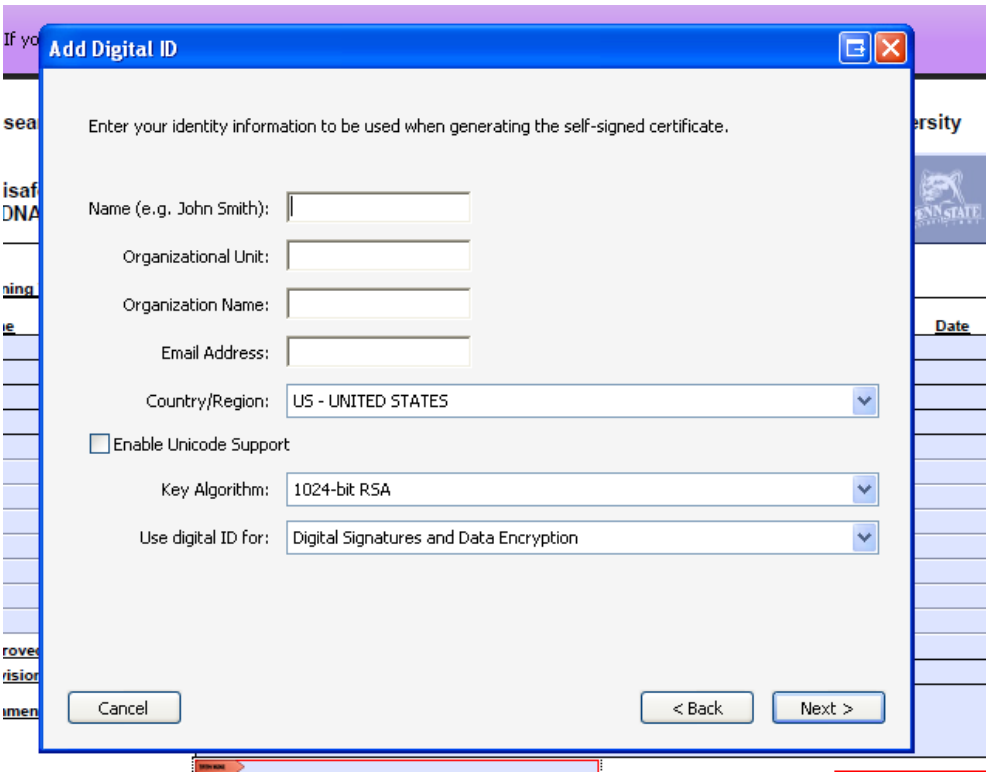
- To digitally sign the document, click within the signature box
- For the first time entering a digital signature, in the “Add Digital ID” box, users have the option to select a new ID from an existing digital ID or create a new digital ID at this time
- Again, if this is the first time creating a digital signature, select “A new digital ID I want to create now”



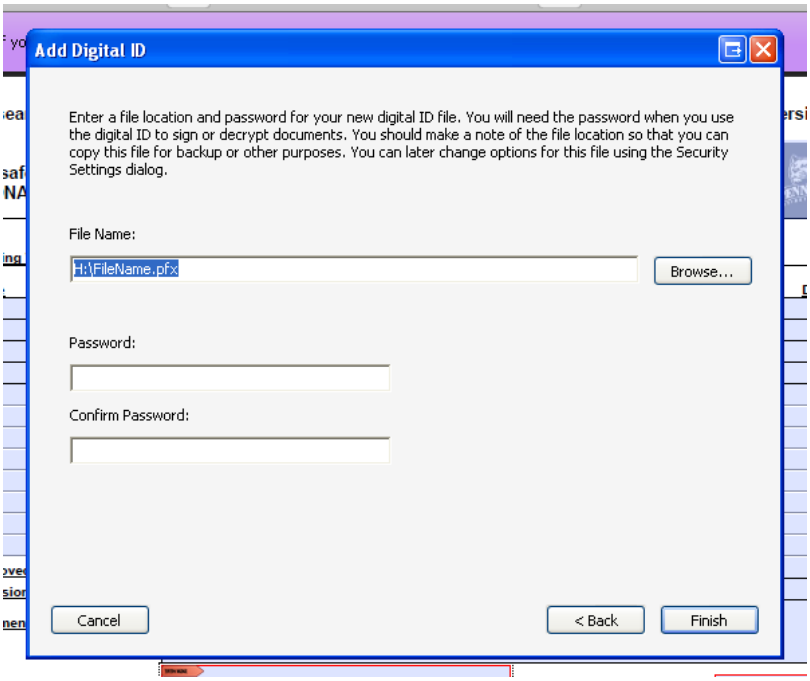
- Select Next and "New PKCS#12 digital ID file" in the following screen, then next again



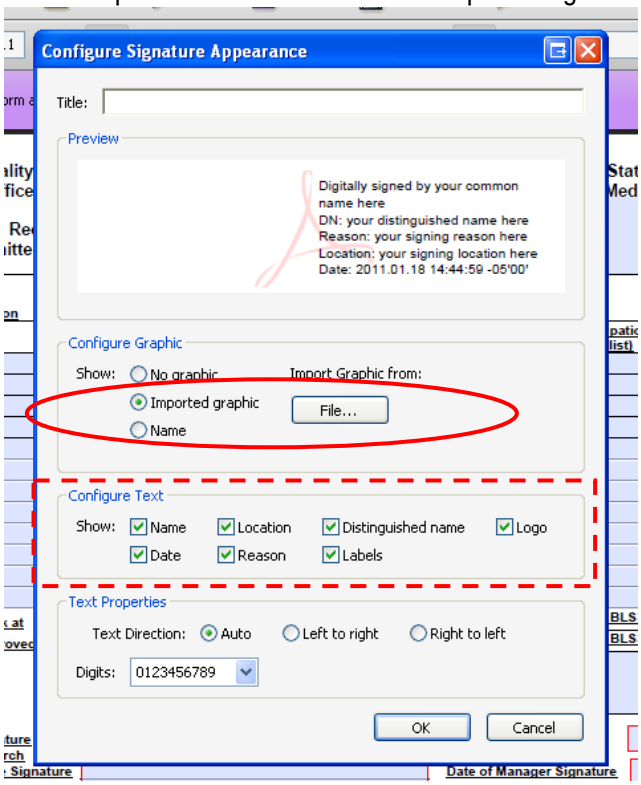
- Enter all the identifying information asked for (without altering the fields "Key Algorithm" or "Use digital ID for"), and select Next



- Select a new file name for the digital ID and create a password of the user's choice – this file name and password will become the method for the user's digital signature from now on



- Select Finish
- To alter the digital signature in any way, select "Appearance" in the pop up box, then select "Create New Appearance"
    - Select "Imported Graphic" in this new window to import a signature from a file



- Users then have the option to select any additional text to appear/not appear next to the signature (see above red dash box)
- Selecting Sign digitally signs the document
- After signing the document using your digital signature, be sure to enter the date in the next field using the format mm/dd/yyyy
- After setting up the digital signature initially, when entering into the signature box, your signature will appear with a box saying "Sign As" followed by a box where you will enter your password. Select "Sign" to sign the document.

3.C.1 De-identifying Documents for Central Adjudication

De-identification is the process by which Personally Identifiable Information (PII) is rendered individually unidentifiable through the removal of such identifiers. PII does not need to be redacted for local adjudication. CRC personnel are responsible to photocopy selected parts of the medical record. For central adjudication, PII is removed from the relevant medical records except for dates of services (for the purposes of accurately identifying study visits, exposures, and clinical events of interest such as, but not limited to, admission, discharge, and treatment/procedure dates) in accordance with DUA to create the DUA dataset. PII that is visible on any part of the DUA dataset must be removed before these documents are scanned and saved to a DVD as secure PDF files. Failure to remove relevant PII will result in the DCC shredding the DVD and the assignment of a protocol violation for the CRC. Two ASSESS-AKI study personnel at the CRC must confirm that all relevant PII has been removed by signing and dating the Event Adjudication Checklist (EA_CHK) before sending the DVD to the DCC for central adjudication.

3.C.2 Personally Identifiable Information (PII)

PII includes health information that identifies a participant, or to which there is a reasonable basis to believe that the information can be used to identify the participant (for example, information contained in a primary health record or a third party claim record).

PII includes the following information:

1. Name

2. All elements of a street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code for areas that contain over 20,000 people

3. All elements of dates (except year) for dates directly related to the individual, (e.g., birth date, admission/discharge dates, date of death); and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.

4. Telephone numbers
5. Fax numbers
6. E-mail address(es)
7. Social security numbers
8. Health record numbers
9. Account numbers
10. Certificate/license numbers
11. License plate numbers, vehicle identifiers, and serial numbers
12. Device identifiers and serial numbers
13. URL addresses
14. Internet Protocol address numbers
15. Biometric identifiers, including finger, and voice prints
16. Full face photographic images and comparable images
17. Any other unique identifying number, characteristic or code except a code used for re-identification purposes

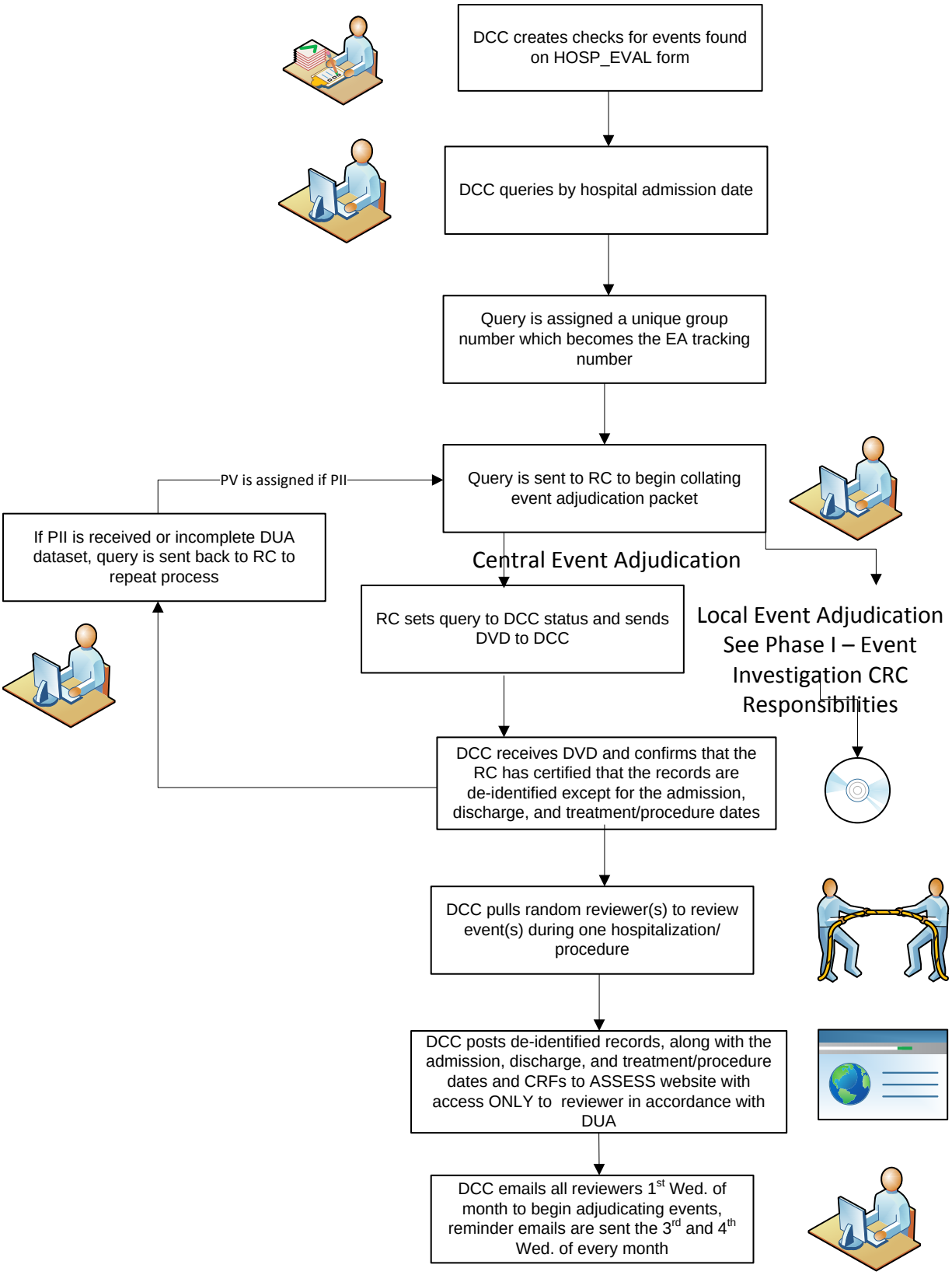
3.C.3 Data Use Agreements (DUA)

A DUA must be signed between the CRC institution and the PSU before the CRC provides a limited data set, which includes only relevant dates of service (for the purposes of accurately identifying study visits, exposures, and clinical events of interest). In addition, a DUA must be signed between the PSU and each physician reviewer before central adjudication may begin.

Changes in reviewers and PIs of the CRCs need to be communicated to the PI of the DCC for Steering Committee approval on the next Steering Committee conference call. All sites, who are exchanging datasets, must be aware of any changes in reviewers. A new PI at a CRC would acknowledge that he has read and understood the DUA (as the original PI did).

3.D *DCC Responsibilities*

The Phase II of the Event Investigation: DCC Responsibilities is diagrammed in more detail below.


DCC creates checks for events found on HOSP_EVAL form
DCC queries by hospital admission date
Query is assigned a unique group number which becomes the EA tracking number
Query is sent to RC to begin collating event adjudication packet
PV is assigned if PII
If PII is received or incomplete DUA dataset, query is sent back to RC to repeat process
Central Event Adjudication
RC sets query to DCC status and sends DVD to DCC
Local Event Adjudication See Phase I – Event Investigation CRC Responsibilities
DCC receives DVD and confirms that the RC has certified that the records are de-identified except for the admission, discharge, and treatment/procedure dates
DCC pulls random reviewer(s) to review event(s) during one hospitalization/ procedure
DCC posts de-identified records, along with the admission, discharge, and treatment/procedure dates and CRFs to ASSESS website with access ONLY to reviewer in accordance with DUA
DCC emails all reviewers 1st Wed. of month to begin adjudicating events, reminder emails are sent the 3rd and 4th Wed. of every month

The DCC plays an integral role in coordinating and managing the flow of events information and documentation between the CRCs and the Events Adjudication Committee (EAC). During the event investigation, the DCC's functions are as follows.

3.D.1 Local Adjudication

1. Create checks for events found on the Hospital/ER Record Evaluation (HOSP_EVAL) form.
2. Query the CRC by hospital admission date.
3. Assign a unique group number to each query, which becomes the EA tracking number.
4. Send a query to the CRC to begin collating an EA packet for each potential event.

3.D.2 Central Adjudication

1. Follow steps 1-4 above related to local adjudication.
2. Receives DVD from the CRC and confirms that the EA packet includes the site-certified DUA dataset and the Event Adjudication Checklist (EA_CHK) is signed and dated by two ASSESS-AKI research coordinators (RC) at the CRC. RC has certified that the records are de-identified except dates of services (for the purposes of accurately identifying study visits, exposures, and clinical events of interest such as, but not limited to, admission, discharge, and treatment/procedure dates) and complete information. If the EA_CHK is not signed and dated, PII is received, or incomplete DUA dataset received, the query is sent back to the CRC to repeat the process. If any relevant PII is received by the DCC in the DUA dataset, DCC will notify the RC about the information, shred the DVD, and assign a protocol violation to the CRC.
3. Add EA tracking number to all pages using Adobe Pro X.
4. Identify a physician reviewer to centrally adjudicate event(s) during one hospitalization/procedure.
5. Post the DUA dataset, data collection forms, and EA forms in accordance with the DUA to the ASSESS-AKI website with access only to the assigned reviewer.
6. Email reviewers on the first Wednesday of the month to begin adjudicating events with reminder emails sent on the third and fourth Wednesday of each month. This process is discussed in more detail in Section 4, Event Adjudication.

4 EVENT ADJUDICATION

4.A *Physician Reviewer*

4.A.1 Physician Reviewer Qualifications

CRCs are responsible for confirming that the physician reviewers have HIPAA and Human Subject certification while reviewing packets. Each CRC will provide two to four reviewers.

- Only MDs and DOs may be reviewers.
- Reviewers may or may not be formal ASSESS-AKI Study key personnel.
- Reviewers must sign a DUA with the PSU in order for the DCC to share the limited data set.
- Reviewers for adult events should have a background in Internal Medicine and/or corresponding relevant subspecialty, including Nephrology, Cardiology, Pulmonary/Critical Care, or General Internal Medicine.
- Reviewers for pediatric events should have a background in Pediatric Medicine with specific experience in Nephrology and/or Critical Care.

4.A.2 Physician Reviewer Responsibilities

All CRCs will undergo event adjudication training of the reviewers and monitoring of event adjudication accuracy as outlined below. For CRCs that have two "certified" local physician reviewers, who successfully passed the training period, all events at that CRC will be reviewed locally. The remaining "uncertified" reviewers must adjudicate events with another "certified" reviewer until they become certified. Two reviewers who are not certified should not adjudicate the same event. For CRCs that do not have two certified reviewers, the events will receive local adjudication as well as central adjudication. It is the responsibility of the reviewers to examine and classify outcome events.

For central adjudication, the DCC will notify the appropriate reviewers that the event packet and the event-specific reviewer forms are posted on the ASSESS-AKI website. Reviewers will have 14 calendar days (starting at the time when the event packet is posted to the website) to review each investigation. For local adjudication, the CRC will have 30 days from the time that the query is sent to the CRC before another query is sent.

Reviewers are responsible for the following:

- Reviewing material, which contains data collection forms, de-identified medical records, and other relevant information, within the timeframe outlined above.
- Determining whether investigated events meet the criteria for ASSESS-AKI Study clinical endpoints.
- Acting as a tie-breaker when other reviewers cannot agree.
- Having access to Adobe Reader version 9.0 or higher.

4.B *Event Adjudication Procedures*

4.B.1 Local Event Adjudication

After potential events are investigated, reviewers examine the participant's event packet, which contains data collection forms, medical records, and other relevant information, to determine whether an event actually occurred.

The procedures for local adjudication of an event are described below. Detailed instructions on how to complete the reviewer forms may be found in Section 6.

1. Log onto the ASSESS website to access the fillable reviewer form(s).

    a. Complete the event-specific reviewer form(s).

EA_CHK	Reviewer Form
AKI	AKIERF
MI	MIERF
IHF	IHERF
CVA/ICH	CERF
PROC	AIPERF/PIPERF

2. Review the Event Adjudication Checklist (EA_CHK), and verify the event classification and data provided by your CRC's RC. For additional information, see Section 4.M.4., Summary of Event Adjudication.

3. Review the event packet.

4. Using standardized criteria, make a decision about whether an event occurred.

    a. Categorize the potential AKI event into pre-renal, acute tubular necrosis (ATN), obstruction, acute interstitial nephritis (AIN), other (specify), or don't know.

    b. Categorize the probability of the cerebrovascular outcome taking place as no event, probable event, or definite event.

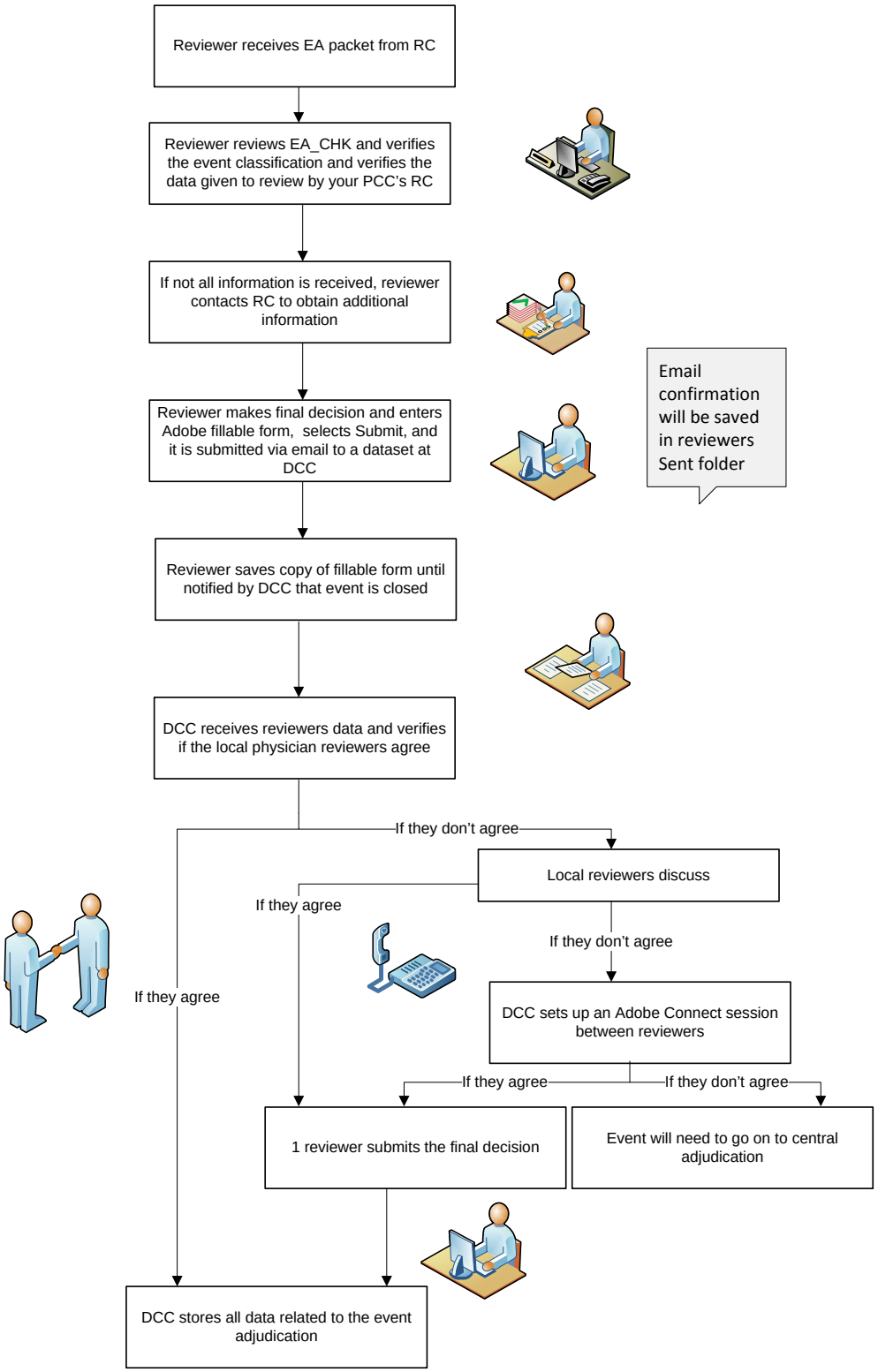
    c. Categorize the probability of the inpatient heart failure outcome taking place as no event, probable event, or definite event.

    d. Categorize the potential MI event as no MI, probable MI, or definite MI.

    e. Check 'Yes' or 'No' that the inpatient procedure was performed.

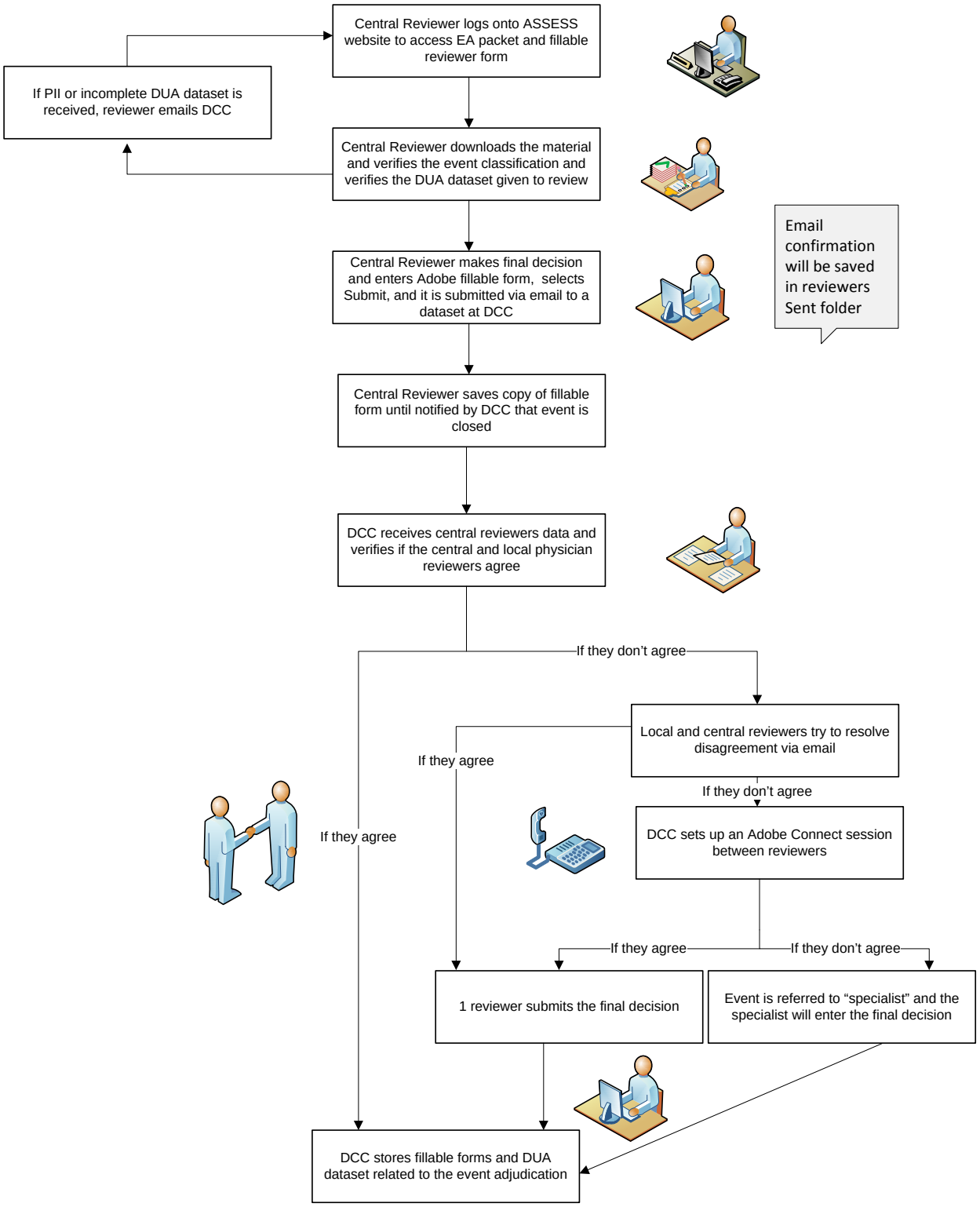
5. Submit the event-specific reviewer form(s) to the DCC via a fillable .pdf file. Save a copy of the fillable form until notified by the DCC that the event is closed.

Phase III – Local Adjudication Review Process and Final Storage of Event Record is diagrammed in more detail below.


Reviewer receives EA packet from RC
Reviewer reviews EA_CHK and verifies the event classification and verifies the data given to review by your PCC's RC
If not all information is received, reviewer contacts RC to obtain additional information
Reviewer makes final decision and enters Adobe fillable form, selects Submit, and it is submitted via email to a dataset at DCC
Email confirmation will be saved in reviewers Sent folder
Reviewer saves copy of fillable form until notified by DCC that event is closed
DCC receives reviewers data and verifies if the local physician reviewers agree
If they don't agree
Local reviewers discuss
If they agree
If they don't agree
If they agree
DCC sets up an Adobe Connect session between reviewers
If they agree
If they don't agree
1 reviewer submits the final decision
Event will need to go on to central adjudication
DCC stores all data related to the event adjudication

4.B.2 Central Event Adjudication

After potential events are investigated, reviewers log onto the ASSESS-AKI website to examine the participant's event packet, which contains the DUA dataset, data collection forms, and other relevant information, to determine whether an event actually occurred. Reviewer event adjudication forms (AKIERF, CERF, IHFERF, and MIERF) are explained in this Section 6 of the MOP. Phase IV – Central Adjudication Review Process and Final Storage of Event Record is diagrammed in more detail below.


Central Reviewer logs onto ASSESS website to access EA packet and fillable reviewer form
If PII or incomplete DUA dataset is received, reviewer emails DCC
Central Reviewer downloads the material and verifies the event classification and verifies the DUA dataset given to review
Central Reviewer makes final decision and enters Adobe fillable form, selects Submit, and it is submitted via email to a dataset at DCC
Email confirmation will be saved in reviewers Sent folder
Central Reviewer saves copy of fillable form until notified by DCC that event is closed
DCC receives central reviewers data and verifies if the central and local physician reviewers agree
If they don't agree
Local and central reviewers try to resolve disagreement via email
If they agree
If they don't agree
DCC sets up an Adobe Connect session between reviewers
If they agree
If they agree
If they don't agree
1 reviewer submits the final decision
Event is referred to "specialist" and the specialist will enter the final decision
DCC stores fillable forms and DUA dataset related to the event adjudication

The procedures for central adjudication of an event are described below. Detailed instructions on how to complete the forms may be found in Section 6.

1. Log onto the ASSESS website to access the Event Adjudication packet and fillable reviewer form.
2. Open your events adjudication folder. Each reviewer will have his/her own folder that is only viewable by him/her.
3. Click on the participant's event tracking number to access the Event Adjudication packet.
4. Complete the event-specific reviewer form(s).

EA_CHK	Reviewer Form
MI	MIERF
IHF	IHERF
CVA/ICH	CERF

5. Download the material, review the Event Adjudication Checklist (EA_CHK), and verify the event classification and DUA dataset given for the review. For additional information, see Section 4.M.4., Summary of Event Adjudication. See Section 4.C., Requesting Additional Records.
6. Review the event packet within 14 calendar days after receipt of the DCC email.
7. Using standardized criteria, make a decision about whether an event occurred.
    a. Categorize the probability of the cerebrovascular outcome taking place as no event, probable event, or definite event.
    b. Categorize the probability of the inpatient heart failure outcome taking place as no event, probable event, or definite event.
    c. Categorize the potential MI event as no MI, probable MI, or definite MI.
    d. The classification of "don't know" will not be used as a result of lack of information or records. "No cerebrovascular event," "not heart failure," or "no MI" should be selected only if the reviewer is confident that the participant likely did not experience any of the conditions or procedures described on the Cerebrovascular Event Reviewer Form (CERF), Inpatient Heart Failure Event Reviewer Form (IHERF), or Myocardial Infarction Event Reviewer Form (MIERF).
8. Submit the event-specific reviewer form(s) to the DCC via a fillable .pdf file. Save a copy of the fillable form until notified by the DCC that the event is closed.

4.C *Requesting Additional Records*

Reviewers will observe the following guidelines when considering the request of additional records.

1. No temporary or provisional reviews will be submitted.

2. Review the Event Adjudication Checklist (EA_CHK) for information regarding availability of records. If a CRC has determined that certain records were unobtainable, a note will indicate this.

3. For local adjudication, the reviewer contacts the RC to obtain additional information. The additional records are to be included in the central adjudication packet.

4. For central adjudication, contact the DCC via email, ASSESS_EVENTS@phs.psu.edu, if there is any problem or any disparity in the DUA dataset that may be encountered when reviewing the EA packet.

    a. Include the participant ID, visit number, and event tracking number in your email. Specification of the desired reports of procedure/test will be provided by the reviewers.

    b. The DCC will contact the CRC to obtain a revised DUA dataset. The reviewers are not to contact the CRC where the participant is enrolled.

    c. If the reviewer identifies another event during the hospitalization, the reviewer should email ASSESS_EVENTS@phs.psu.edu with the participant ID, visit number, and type of event.

4.D *If Records Are Not Readable*

If records are not readable, the reviewer should contact ASSESS_EVENTS@phs.psu.edu. The DCC will request clearer records. If clearer records are not available, the DCC will inquire if the reviewer can make her/his best guess with the information available. If the information needed to make a decision of definite or probable is not available, it would be adjudicated as not having an event.

4.E *DCC Responsibilities*

4.E.1 Event Adjudication Training

1. The DCC will select the first 20 cardiovascular events from each CRC to be adjudicated by one central reviewer and two local reviewers.

    a. Cardiovascular events are defined as myocardial infarction, inpatient heart failure, ischemic stroke, intracranial hemorrhage, and PVD (blockage in the arteries of the arms, legs, and abdomen).

    b. AKI and procedures are not considered to be cardiovascular events.

2. At each local site, the first 20 cardiovascular events will be reviewed by two local adjudicators and one central adjudicator.

    a. Two reviewers are needed at each CRC to ensure equal participation and inter-rater reliability and consistency with central adjudication.

3. For an adjudicator to pass the training phase, he/she must have at least 80% concordance with another adjudicator.

4. Since local adjudicators and central adjudicators may be the same (i.e., a local adjudicator may serve as central adjudicator for a different site), the qualification threshold for independent adjudication is the same for both types of adjudicators.

5. There will be three adjudicators for each of these first 20 cardiovascular events.

6. Concordance will be judged for any two adjudicators who agree. It does not require all three to agree.

7. If all three reviewers agree, no further review of that event is required and all three reviewers receive concordance credit for the event since the initial diagnosis and the final diagnosis agree.

8. If only two of the three agree, a conference call will be arranged. Refer to 4.E. below.

9. If they all agree on the conference call, that will be the final diagnosis, and the reviewer(s) whose initial diagnosis is the same as the final diagnosis receive concordance credit for the event. However, the reviewer with a different initial diagnosis will not receive concordance credit for this event.

10. If they cannot agree on the conference call, the event will be referred to a specialist (neurologist or cardiologist) for final resolution. The reviewer(s) whose initial diagnosis is the same as the final diagnosis made by the specialist receive concordance credit for the event.

11. After review of 20 cardiovascular events, adjudicators scoring 80% or greater concordance will have passed and become “certified.”

12. If a reviewer does not achieve 80% concordance after 20 events, he/she will need to complete an additional 10 cardiovascular event reviews and achieve 80% concordance on these events.

13. Local reviewers may achieve passing scores, become "certified," at different times. Only when there have been two local reviewers achieving passing scores can that site relay on local adjudication. The remaining reviewers must adjudicate events with another "certified" reviewer until they become certified. Two reviewers who are not certified should not adjudicate the same event.

14. Events in which the local reviewers serve as central adjudicators for other sites would be counted as part of their training events.

4.E.2 Diagnostic Agreement

The reviewers' answers to a single question per form, with the exception of the Procedure Event Reviewer Form must match in order to have diagnostic agreement.

- For the Acute Kidney Injury Event Reviewer Form (AKIERF), the response to Q1190 must match.
- For the Cerebrovascular Event Reviewer Form (CERF), the response to Q1000 must match. If Q1020 is marked 'Yes', the response to Q1040 must also match.
- For the Inpatient Heart Failure Event Reviewer Form (IHFERF), the response to Q1130 must match.
- For the Myocardial Infarction Event Reviewer Form (MIERF), the response to Q1120 must match.
- For the Adult/Pediatric Inpatient Procedure Event Reviewer Form (AIPERF/PIPERF), all of the answers must match.

4.E.3 Central Adjudication Procedure

The DCC will support all central adjudication activities. All questions or concerns with the process should be relayed directly to the DCC via email to ASSESS_EVENTS@phs.psu.edu. The DCC is specifically responsible for the following:

1. Acquire signed DUAs between the ASSESS-AKI CRCs and PSU and another between the PSU and each reviewer.

2. Identify a random physician reviewer to review event(s) during one hospitalization/procedure for central adjudication.

3. Post the DUA dataset to the ASSESS website with access only to the reviewer.

4. Email reviewers on the first Wednesday of the month to begin adjudicating events with reminder emails sent on the third and fourth Wednesday of each month.

5. Verify that the reviewers agree or disagree.

6. If there is disagreement, refer to Section 4.F., Disagreement Resolution.

7. Because reviewers may need to resolve disagreements even after they enter their individual

reviews, the reviewers will not destroy the events records for any investigation until notified by the DCC. Reviewers should destroy the files for closed reviews that they have printed or saved.

8. The DCC will store all data related to the central adjudication and the reviewer forms related to local adjudication.

4.F *Audit and Disagreement Resolution*

4.F.1 Audit

Ten percent of the new locally adjudicated events will be centrally adjudicated each quarter (January, April, July, and October). The events to be audited will be randomly selected prior to any disagreement resolution. Those events not selected to be audited will proceed with disagreement resolution, if necessary. Those events selected for the audit will not undergo disagreement resolution. These will be in the audit pool for central adjudication. If there is disagreement after central adjudication, one disagreement resolution form will be submitted with the decision of all three reviewers.

4.F.2 Disagreement Resolution

If there is a disagreement between reviewers:

1. The DCC will notify the reviewers by email and indicate which specific endpoint(s) was in disagreement.

2. The reviewers will have 14 days to consider the case and consult with each other about the endpoint(s) in disagreement. The dissenting reviewer should review the event independently and see if s/he is agreeable to changing her/his decision. If the decision is changed, the dissenting reviewer submits a disagreement form. If the decision is not changed, the dissenting reviewer should email the other reviewers to discuss. If consensus is reached by the reviewers, one reviewer will submit a disagreement resolution form.

3. If no consensus is reached, the DCC will schedule an Adobe Connect session between the reviewers to try to reach consensus with the call moderated by QCC and DCC representatives. The QCC representative should not be from the CRC where the event occurred.

4. If consensus is reached after the Adobe Connect session, one reviewer submits the final decision via a disagreement resolution form to the DCC, and the DCC verifies the final dataset in the application.

5. If no consensus is reached after the Adobe Connect session, the event will be referred to a neurologist or cardiologist to act as the final reviewer, or "Specialist."

    a. The Specialist will make a decision and submit the final decision to the DCC via a disagreement resolution form.

    b. The DCC will verify the final dataset in the application.

6. Because reviewers may need to resolve disagreements even after they enter their individual reviews, the reviewers will not destroy any event records and event adjudication forms of any investigation until notified by the DCC.

7. Reviewers should destroy the files for closed reviews that they have printed or saved.

4.G *New Reviewer*

A new reviewer may be added to replace a reviewer or as an additional reviewer to the CRC. Training of the new reviewer is the responsibility of the CRC.

If the new reviewer is replacing a reviewer, the new reviewer may review the events that the previous reviewer had reviewed locally EXCEPT those events that are closed for review, centrally adjudicated, or under disagreement resolution.

The DCC will delete the forms submitted by the previous reviewer and replace them with the forms of the same events completed by the new reviewer submitting forms. The DCC will not delete the forms submitted by the previous reviewer that are closed for review, centrally adjudicated, or under disagreement resolution.

4.H *Adjudication Criteria*

Below is the subset of events that will require physician adjudication. See Section 2 for all of the events of interest to the ASSESS-AKI Consortium.

- *Cardiovascular Events:* Acute Coronary Syndrome, Inpatient Heart Failure
- *Cerebrovascular Events:* Ischemic Stroke, Intracranial Hemorrhage, Cerebral Infarction

4.I *Criteria for Renal Events*

The Acute Kidney Injury Event Reviewer Form (AKIERF) is used for renal events. Because only DCC-confirmed AKI events based on measurements of serum creatinine will be adjudicated, the review will focus on the type of AKI as AKI Pre-Renal, AKI Acute Tubular Necrosis (ATN), Obstruction-induced AKI, Acute Interstitial Nephritis (AIN), or AKI Other.

Participants have labs drawn at twelve-month intervals for assessment of renal function to determine CKD status. Participants are screened at six-month intervals for development of ESRD. Participants have all serum creatinine values during any hospitalization recorded for assessment of incident or recurrent AKI episodes.

4.I.1 Definitions

Incident CKD will be defined as at least a 25% reduction in level of eGFR compared with baseline (i.e., before the index hospitalization) AND achieving CKD Stage 3 or worse among participants without pre-existing CKD at the index hospitalization. We will determine this using the serum creatinine value obtained at each annual visit.

Progression of CKD will be defined at least a 50% reduction in level of eGFR compared with baseline kidney function OR progressing to CKD Stage 5 among participants with pre-existing CKD at the index hospitalization (defined as a baseline eGFR <60 ml/min/1.73m^2). We will determine this using the serum creatinine value obtained at each annual visit.

Development of ESRD will be defined as meeting any of the following criteria: (1) receipt of any outpatient dialysis after V3M; (2) death while receiving inpatient dialysis lasting ≥28 days; and/or (3) receipt of a kidney transplant. This outcome will be assessed on an interval basis every six months by direct questioning of the participant or review of medical records for hospitalization. Death while receiving new (i.e., in the absence of prior chronic outpatient dialysis) inpatient dialysis lasting <28 days or receipt of new inpatient dialysis lasting <28 days and being discharged from the hospital off dialysis will be considered dialysis-requiring AKI.

Example: Participant is discharged (at any day of dialysis) and receives outpatient Hemodialysis; ESRD is included in the diagnoses. At the next visit (6-month or yearly), if the participant is still on dialysis, then ESRD is confirmed; if off dialysis, we obtain the last date of dialysis and participant is checked as "recovered renal function." These latter cases are subsequently switched from ESRD to AKI.

Incident or Recurrent Episodes of AKI will be assessed using available laboratory results obtained during hospitalizations occurring throughout the follow-up period. Episodes of AKI will initially use the same criteria as for entry into ASSESS-AKI (i.e., change in serum creatinine concentration using the peak inpatient value compared with the most recent pre-admission ASSESS-AKI Study serum creatinine result). If the serum creatinine rose by at least 0.3 mg/dL or 50% from the most recent preadmission ASSESS-AKI serum creatinine value, the participant will be classified as sustaining an AKI episode. If the participant was initially a control, it will be an incident AKI episode. If the participant was originally an AKI case from the index hospitalization, it will be considered a recurrent episode of AKI.

Furthermore, all laboratory-defined AKI episodes (incident or recurrent) will be further subclassified into a type of AKI. The definitions for the five types of AKI are outlined below.

4.I.2 Criteria for Acute Tubular Necrosis (ATN)

Acute tubular necrosis (ATN) will be considered the etiology of AKI when one or more of the following are present:

- Indication that the cause of AKI was ATN in either the progress notes, nephrology consult notes, or discharge summary
- Urine microscopy by a nephrologist revealing any of the following:
  - Muddy brown granular casts
  - Epithelial cell casts
  - Free renal tubular epithelial cells

  Or
- One or more acute dialysis treatments in a patient not previously receiving maintenance dialysis, and no other cause of AKI is listed.

Also, if renal imaging is available, there should be no evidence of significant urinary tract obstruction.

4.I.3 Criteria for Pre-renal AKI

Pre-renal AKI will be considered the etiology of AKI when one or more of the following are present:

- Indication that the cause of AKI was pre-renal in either the progress notes, nephrology consult notes, or discharge summary
- Urine microscopy by a nephrologist does NOT reveal any of the following:
  - Muddy brown granular casts
  - Epithelial cell casts
  - Free renal tubular epithelial cells
- Fractional excretion of sodium (FeNa) is documented as < 1%

Also, if renal imaging is available, there should be no evidence of significant urinary tract obstruction.

4.I.4 Criteria for Obstruction-induced AKI

Obstruction will be considered the etiology of AKI when one or more of the following are present:

- Indication that the cause of AKI was urinary tract obstruction in either the progress notes, nephrology consult notes, or discharge summary
- Renal imaging demonstrates evidence of significant urinary tract obstruction

4.I.5 Criteria for Acute Interstitial Nephritis (AIN)

Acute interstitial nephritis (AIN) will be considered the etiology of AKI when one or more of the following are present:

- Indication that the cause of AKI was AIN in either the progress notes, nephrology consult notes, or discharge summary
- Urine microscopy by a nephrologist does reveal the following:
  - White blood cell casts (listed in Q1110D on AKIERF)

Also, if renal imaging is available, there should be no evidence of significant urinary tract obstruction.

4.I.6 Criteria for "Other" as Cause of AKI

Other will be considered the etiology of AKI when ALL of the following are true:

- There is no consensus or indication of the etiology of AKI in the progress notes, nephrology consult notes, or discharge summary
- Urine microscopy by a nephrologist is not performed or recorded
- There is no documentation of FeNa; or the FeNa is between 1 and 2%
- There is no renal imaging available or it is available and does not indicate evidence of significant urinary tract obstruction
- A specific etiology other than those defined above, such as glomerulonephritis or atheroembolic disease, is listed in the progress notes, nephrology consult notes or discharge summary

4.J *Criteria for Cardiovascular Events*

Participants are screened at six-month intervals for hospitalization using the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS) form. The Myocardial Infarction Event Reviewer Form (MIERF) is used for myocardial infarction (MI) events.

4.J.1 Definition for Acute Coronary Syndrome (ACS)

Acute Coronary Syndrome (ACS) will be documented when both of the following are present:

- Chest pain or other symptoms attributable to myocardial ischemia of at least five minutes' duration and occurring either at rest or with minimal exertion or provocation.
- Objective evidence of myocardial ischemia consisting of at least one of the following:
  - Transient or fixed, new or presumed new ST segment depression of at least 1 mm in at least two contiguous ECG leads
  - Transient or fixed, new or presumed new T wave inversion in at least two contiguous ECG leads
  - Troponin I elevation above the upper limit of normal (ULN).

Events meeting the above classification but satisfying the definitions of myocardial infarction (MI) will be classified as MI. Adjudicators may consider additional clinical data (e.g. the results of coronary angiography) in defining the episode as cardiac or noncardiac in origin. As false positive ECG and enzyme abnormalities can occur, the adjudicators may reject the diagnosis of ACS despite the presence of ECG or enzyme abnormalities.

4.J.2 Criteria for Acute Myocardial Infarction

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of rise and/or fall of troponin with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
- Symptoms of ischemia;
  - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood with symptoms

suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy.

- Pathological findings of an acute MI.

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4.J.3 ECG Criteria

ASSESS-obtained ECGs from the most recent ASSESS in-person visit, prior ECG records from the 48 hours before until 48 hours after the event, and the admission and/or prior to discharge ECGs from the CRC will be obtained and provided to the physician reviewer to evaluate for acute ECG changes.

4.J.4 Classification Algorithms

For MI, the following tables summarize the classification algorithms:

Table 1. Algorithm for Hospitalized MI –

Cardiac Pain or Other Cardiac Ischemic Clinical Presentation

	Peak Troponin I Classification		
ECG Pattern	Abnormal	Normal/Equivocal	Missing
Evolving Diagnostic ECG (Evolution of major Q-wave)	Definite MI	Definite MI	Definite MI
Positive ECG (Evolution of ST Elevation with or without Q-wave OR new LBBB)	Definite MI	No MI	Definite MI
Non-specific ECG (Evolution of ST-T Depression/ inversion alone OR evolution or minor Q-waves alone)	Definite MI	No MI	No MI
ECG Negative for Ischemia Normal, Absent, Uncodable, or Other	Definite MI	No MI	No MI

NOTE: Cases in which the clinical presentation is consistent with acute MI and the participant undergoes emergent successful primary recanalization will be classified as a definite MI, independent of the above criteria.

Table 2. Algorithm for Hospitalized MI – Cardiac Pain Absent

	Troponin I Classification		
ECG Pattern	Abnormal	Normal/Equivocal	Missing
Evolving Diagnostic ECG (Evolution of major Q-wave)	Definite MI	Definite MI	Definite MI
Positive ECG (Evolution of ST Elevation with or without Q-wave OR new LBBB)	Definite MI	No MI	Possible MI
Non-specific ECG (Evolution of ST-T Depression/ inversion alone OR evolution or minor Q-waves alone)	Definite MI	No MI	No MI
ECG Negative for Ischemia Normal, Absent, Uncodable, or Other	Definite MI	No MI	No MI

NOTE: Cases in which the clinical presentation is consistent with acute MI and the participant undergoes emergent successful primary recanalization will be classified as a definite MI, independent of the above criteria.

4.K *Criteria for Hospitalization for Acute Heart Failure*

The Inpatient Heart Failure Event Reviewer Form (IHFERF) is used for acute heart failure events for adult participants who have a primary discharge diagnosis of heart failure, not secondary heart failure related to another primary diagnosis such as pneumonia or from a procedure.

Ejection fraction is not a heart failure criterion because ASSESS-AKI is using clinical presentation. Hospitalization for clinical symptoms of acute heart failure (AHF) (dyspnea on exertion or rest, paroxysmal nocturnal dyspnea, and/or orthopnea) with at least one of the following objective findings:

Heart Failure Criteria

Diagnosis of chronic heart failure (CHF) requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

Minor criteria are acceptable only if they cannot be attributed to another medical condition (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome, pneumonia). Tachycardia is assessed around the time of the physical exam.

Major Criteria

- Paroxysmal nocturnal dyspnea
- Neck vein distention
- Rales
- Radiographic cardiomegaly (enlarged heart size on chest radiography)
- Acute pulmonary edema
- S3 gallop
- Increased central venous pressure (>16cm H_2O at right atrium)
- Hepatojugular reflux
- Weight loss >4.5 kg in 5 days in response to treatment

Minor Criteria

- Bilateral ankle edema
- Nocturnal cough
- Dyspnea on ordinary exertion
- Tachycardia (heart rate >120 beats/min)
- Pleural effusion
- Hepatomegaly
- Decrease in vital capacity by one third from maximum recorded

4.L *Criteria for Inpatient Procedure Events*

The following inpatient procedures will utilize the Adult Inpatient Procedure Event Reviewer Form (AIPERF).

- Coronary artery bypass surgery
- Percutaneous coronary intervention
- Peripheral artery intervention
- Lower extremity/ digit amputation (more than one digit)
- Carotid artery revascularization (angiography, stenting, carotid endarterectomy)
- Implantation of cardioverter/defibrillator
- Abdominal aortic aneurysm repair

The following inpatient procedures will utilize the Pediatric Inpatient Procedure Event Reviewer Form (PIPERF).

- Cardiac surgery with cardiopulmonary bypass
- Cardiac surgery without cardiopulmonary bypass
- Catheterization procedure: diagnostic
- Catheterization procedure: interventional
- Implantation of cardioverter/defibrillator

4.M *Criteria for Cerebrovascular Events*

The Cerebrovascular Event Reviewer Form (CERF) is used for cerebrovascular events for adult participants. All hospitalizations will be screened for stroke by looking for ICD-9/10 diagnosis codes for stroke (ischemic or hemorrhagic). Refer to the Reference Cards for the ICD-9/ICD-10 codes. Any charts found in this manner will be abstracted for stroke evaluation.

All confirmed cerebrovascular events that are abstracted will be classified further by screening for intracranial hemorrhage (intracerebral bleeding, subarachnoid hemorrhage, and subdural hematoma). If these are negative, they will receive an ischemic stroke determination.

4.M.1 Definitions

Definition of major neurological signs and symptoms:

1. Hemiparesis involving two or more body parts
2. Homonymous hemianopsia
3. Aphasia
4. Neglect

Definition of minor neurological signs and symptoms:

1. Diplopia
2. Vertigo or gait disturbance
3. Dysarthria, dysphagia, or dysphonia
4. Hemisensory loss involving two or more body parts
5. Ataxia

4.M.2 Criteria for Intracerebral Hemorrhage

1. Autopsy or surgery proven intra-parenchymal hemorrhage or subarachnoid hemorrhage.

OR

2. Sudden or rapid onset of severe headache with or without any neurologic signs or symptoms lasting for more than 24 hours or until the participant died, plus evidence of intraparenchymal hematoma or evidence of subarachnoid hemorrhage seen on head CT or MRI. Intraventricular hemorrhage may occur with intra-parenchymal hemorrhage or subarachnoid hemorrhage and does not affect classification.

4.M.3 Likelihood of Stroke Determination

Definition of Definite Stroke

1. Sudden or rapid onset of one major or two minor neurologic signs or symptoms within a single vascular territory lasting for more than 24 hours or until the participant died, without alternative etiology. CT or MRI finds may be equivocal or test results not available.

OR

2. Symptoms consistent with an acute ischemic stroke and either (A) autopsy proven nonhemorrhagic infarction in the brain or (B) CT or MRI demonstration of an acute infarct (e.g., hypoattenuation on CT, increased signal on MRI T2, FLAIR, or DWI) in the appropriate vascular territory.

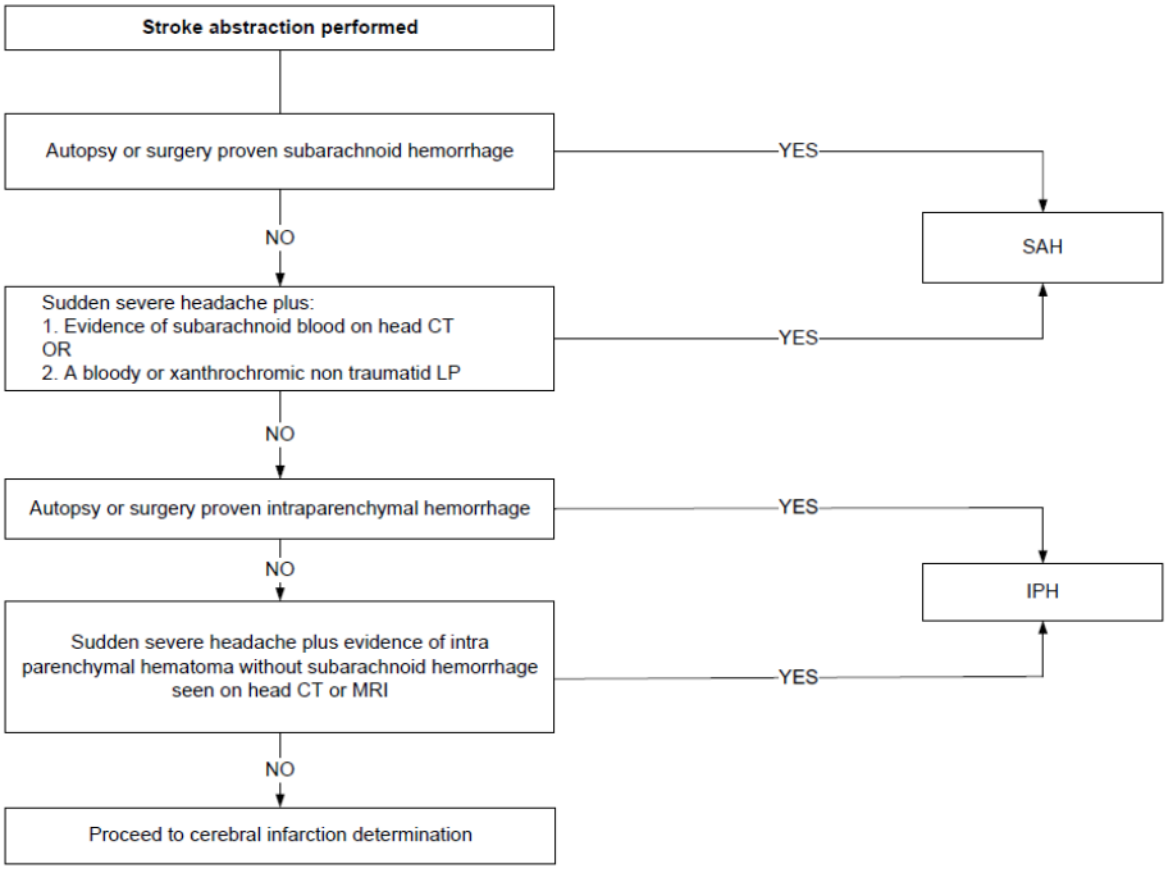
Definition of Probable Stroke

1. Sudden or rapid onset of one major or two minor neurologic signs or symptoms within a single vascular territory without an alternative etiology but where the duration of symptoms is not confirmed lasting for more than 24 hours or until the participant died. CT or MRI may be equivocal or not available.

OR

2. Sudden or rapid onset of one major or two minor neurologic signs or symptoms within a single vascular territory lasting for more than 24 hours or until the participant died but where it is unclear if there is an alternative etiology. CT or MRI may be equivocal or not available.

The schematic below provides a general flow for evaluating possible intracranial hemorrhage and ischemic strokes/cerebral infarctions



4.M.4 Summary of Event Adjudication

Event Type	cal/CentralAdjudication	Adult/Peds	EA_CHK	Reviewer Form
Acute kidney injury (AKI)	AKI determined by DCC; Local – etiology of AKI	Adults/Peds	AKI	AKIERF
Myocardial infarction (MI)	Local/Central	Adults	MI	MIERF
Inpatient heart failure (IHF)	Local/Central	Adults/Peds	IHF	IHERF
Ischemic stroke, TIA	Local/Central	Adults/Peds	CVA/ICH	CERF
Hemorrhage stroke, ICH	Local/Central	Adults/Peds	CVA/ICH	CERF
PVD: blockage in the arteries of the arms, legs, abdomen	Local	Adults	PROC	AIPERF
PVD: peripheral artery intervention	Local	Adults	PROC	AIPERF
PVD: lower extremity/digit amputation	Local	Adults	PROC	AIPERF
Coronary artery bypass surgery	Local	Adults	PROC	AIPERF
Percutaneous coronary intervention	Local	Adults	PROC	AIPERF
Carotid artery revascularization	Local	Adults	PROC	AIPERF
Abdominal aortic aneurysm repair	Local	Adults	PROC	AIPERF
Implantation of cardioverter/ defibrillator	Local	Adults/Peds	PROC	AIPERF/ PIPERF
Cardiac surgery without cardiopulmonary bypass	Local	Peds	PROC	PIPERF
Catheterization procedure: diagnostic or interventional	Local	Peds	PROC	PIPERF

5 REVIEWER FORMS

5.A *Adult Inpatient Procedure Event Reviewer Form (AIPERF)*

Purpose: This is an Event Adjudication Reviewer form used to determine the occurrence of an adult inpatient procedure event.

Who: An ASSESS-AKI Event Adjudication Reviewer completes the form

When: As necessary when assigned a possible adult inpatient procedure event to review.

Form Instructions:

Questions 1000-1060. Answer 'Yes' or 'No' to each of the possible inpatient procedures.

Question 1030. Answer 'Yes' if a lower extremity has been amputated. Answer 'Yes' if more than one digit is amputated. Answer 'No' if one digit is amputated.

5.B *Acute Kidney Injury Event Reviewer Form (AKIERF)*

Purpose: This is an Event Adjudication Reviewer form used to determine the occurrence and documentation of acute kidney injury.

Who: An ASSESS-AKI Event Adjudication Reviewer completes the form

When: As necessary when assigned a possible acute kidney injury event to review

Form Instructions:

Question 1000. If there is documentation in the progress notes or discharge summary that the participant experienced acute kidney injury, proceed to Q1010. If Q1000 is answered 'No' or 'Don't know', proceed to Q1060.

Questions 1010-Q1050. Indicate the cause of the AKI indicated in the progress notes, nephrology consult notes, or discharge summary by answering each question 'Yes' or 'No'. If the response to Q1050 is 'Other', please specify the cause of the AKI in Q1050D.

Question 1060. Indicate there is documentation of a urine microscopy by a nephrologist.

Questions 1070. If there is documentation of inpatient acute dialysis, complete Q1080-Q1130. If Q1070 is answered 'No' or 'Don't know', proceed to Q1140.

Questions Q1080-Q1130. Record the start date of the first dialysis and stop date for the last dialysis. If the month and/or day is unknown, record 98 in Q1080, Q1090, Q1110 and/or Q1120. If the year is unknown record 9898 in Q1080 and/or Q1130.

Questions 1140-1170. Answer 'Yes' or 'No' to each modality of dialysis listed.

Question 1190. Indicate how you would characterize the event using all of the information available in the medical record. The response to this question must be concordant with the response of the other reviewer.

5.C *Cerebrovascular Event Reviewer Form (CERF)*

Purpose: This is an Event Adjudication Reviewer form used to determine the occurrence of a cerebrovascular event.

Who: An ASSESS-AKI Event Adjudication Reviewer completes the form

When: As necessary when assigned a possible cerebrovascular event to review

Form Instructions:

DO NOT COMPLETE THIS FORM FOR EVENTS COLLECTED ON PEDIATRIC PARTICIPANTS

Question 1000. Indicate how you would characterize the event using all of the information available in the medical record. If Q1000 is answered 'No cerebrovascular event', stop completion of the form.

Questions 1010. If the participant experienced a cerebrovascular event, indicate the type of cerebrovascular event. Select only one response to Q1010. If the response for Q1010 is 'Other', please specify the type in Q1010D.

Question 1020. If there was a second cerebrovascular event during the hospitalization, complete Q1030. If Q1020 is answered 'No', proceed to Q1050.

Question 1030. If the participant experienced a second cerebrovascular event, indicate the type of cerebrovascular event. Select only one response for Q1030. If the response to Q1030 is Other, please specify the type in Q1030D.

5.D *Cerebrovascular Event Reviewer Disagreement Resolution Form (CERF_DISC)*

Purpose: This is an Event Adjudication Reviewer form used when a disagreement exists to record the final consensus of a(an) cerebrovascular event(s).

Who: An ASSESS-AKI Event Adjudication Reviewer completes the form

When: As necessary when assigned a cerebrovascular event disagreement to review

Form Instructions:

DO NOT COMPLETE THIS FORM FOR EVENTS COLLECTED ON PEDIATRIC PARTICIPANTS

Question 1060. Indicate the final consensus of the group. If Q1000 is answered 'No cerebrovascular event', stop completion of the form.

Question 1070. If the participant experienced a second cerebrovascular event, indicate the final consensus of the group.

5.E *Inpatient Heart Failure Event Reviewer Form (IHFERF)*

Purpose: This is an Event Adjudication Reviewer form used to determine the occurrence of inpatient heart failure event.

Who: An ASSESS-AKI Event Adjudication Reviewer completes the form

When: As necessary when assigned a possible inpatient heart failure event to review.

Form Instructions:

Question 1000. COMPLETE FOR EVENTS COLLECTED ON ADULT PARTICIPANTS. Indicate if there is documentation of clinical symptoms such as dyspnea on exertion or rest, paroxysmal nocturnal dyspnea, and/or orthopnea.

Question 1010. COMPLETE FOR EVENTS COLLECTED ON PEDIATRIC PARTICIPANTS. Indicate if there is any documentation of radiographic evidence of pulmonary edema or pulmonary congestion.

Questions 1020-1080. Answer 'Yes', 'No', or 'Don't know' to each of the exam findings listed. At least two of the indicated physical exam findings should be answered 'Yes'.

Question 1050. DO NOT COMPLETE FOR EVENTS COLLECTED ON PEDIATRIC PARTICIPANTS.

Questions 1090-1110. Answer 'Yes', 'No', or 'Don't know' to each of the evidence listed.

Question 1120. Indicate how you would characterize the event using all of the information available in the medical record. The response to this question must be concordant with the response of the other reviewer.

5.F *Inpatient Heart Failure Event Reviewer Disagreement Resolution Form (IHFERF_DISC)*

Purpose: This is an Event Adjudication Reviewer form used when a disagreement exists to record the final consensus of an inpatient heart failure event.

Who: An ASSESS-AKI Event Adjudication Reviewer completes the form

When: As necessary when assigned an inpatient heart failure event disagreement to review

Form Instructions:

Question 1150. Indicate the final consensus of the group.

5.G *Myocardial Infarction Event Reviewer Form (MIERF)*

Purpose: This is an Event Adjudication Reviewer form used to determine the occurrence of myocardial infarction event.

Who: An ASSESS-AKI Event Adjudication Reviewer completes the form

When: As necessary when assigned a possible myocardial infarction event to review

Form Instructions:

DO NOT COMPLETE THIS FORM FOR EVENTS COLLECTED ON PEDIATRIC PARTICIPANTS

Question 1000. If Troponin I values are available complete Q1030, otherwise proceed to Q1090.

Question 1070. If the participant underwent coronary revascularization before the peak Troponin I value complete Q1080, otherwise proceed to Q1090.

Questions 1080. If the participant underwent coronary revascularization before the peak Troponin I value, indicate the type. Select only one response to Q1080. If the response for Q1080 is 'Other', please specify the type in Q1080D.

Question 1090. If symptoms consistent with acute cardiac ischemia were present complete Q1100. If symptoms were not present proceed to Q1110. If it is unknown whether symptoms were present proceed to Q1120.

Question Q1100. If symptoms consistent with acute cardiac ischemia were present select only one response in the table and proceed to Q1120.

Question Q1110. If symptoms consistent with acute cardiac ischemia were not present select only one response in the table and proceed to Q1120.

Question 1120. Indicate how you would characterize the event using all of the information available in the medical record. The response to this question must be concordant with the response of the other reviewer.

5.H *Myocardial Infarction Event Reviewer Disagreement Resolution Form (MIERF_DISC)*

Purpose: This is an Event Adjudication Reviewer form used when a disagreement exists to record the final consensus of a myocardial infarction event.

Who: An ASSESS-AKI Event Adjudication Reviewer completes the form

When: As necessary when assigned a myocardial infarction event disagreement to review

Form Instructions:

Question 1140. Indicate the final consensus of the group.

5.I *Pediatric Inpatient Procedure Event Reviewer Form (PIPERF)*

Purpose: This is an Event Adjudication Reviewer form used to determine the occurrence of a pediatric inpatient procedure event.

Who: An ASSESS-AKI Event Adjudication Reviewer completes the form

When: As necessary when assigned a possible pediatric inpatient procedure event to review.

Form Instructions:

Questions 1000-1040. Answer 'Yes' or 'No' to each of the possible inpatient procedures.

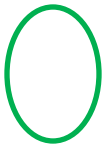
5.J *Fillable Instructions for Reviewer Forms*

1. Go to the ASSESS website and in the following location you can download the Reviewer Forms
    a. Home: Committees: Event Adjudication Committee: Reviewer Forms

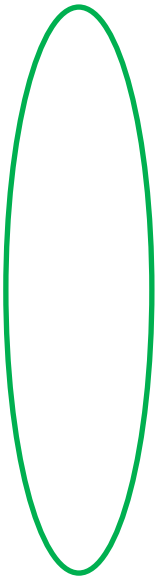
2. When you open the Fillable packet, it will open for you in Adobe Reader (or Acrobat if you have the full version on your machine)

3. Fields in red are required for submission, so we can review each field for completeness:

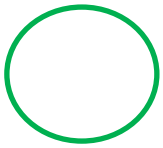
    a. Complete the Participant ID which should match the crf/data collection forms for this participant, starting with Protocol (1 for adult and 2 for peds)
        i. Note: if this is for central adjudication, the entire Participant ID will NOT match the actual Participant ID; simply complete the fields as prompted below.



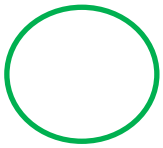
The site number will be in a drop down list, select the down arrow and choose the site for the participant you are doing the adjudication on (i.e., 1B – Yale - Cincinnati, 1C – Yale - London, 1D- Yale –Montreal, 1E – Yale - New Haven, 2A – Vanderbilt, 3A- Kaiser - Oakland, 3B – Kaiser – San Francisco, 3C- Kaiser – Walnut Creek, 3E – Kaiser - Hayward, 4A – University of Washington – Harborview). Note: if this is a central adjudication, this site number will NOT match your own site number. You can find the participant's site number on the EA_CHK at the time of posting.



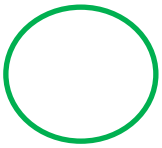
b. Participant Id is the 4 digit number starting with either 1000-4999 or 5000-9999.
    i. Note: if this is central adjudication, please use 9999 for ALL reviewer forms. The DCC will correct the participant ID when inserted into the final dataset.



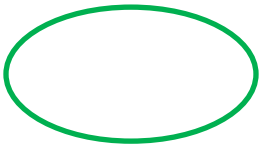
c. Participant Initials should match the crf/data collection forms for this participant:



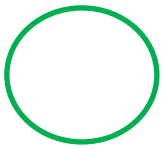
d. Visit Number should match the crf/data collection forms; this is when the event took place (i.e., V6M, V12M, V18M, V24M, etc.)



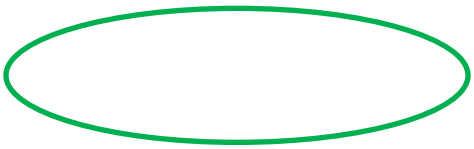
e. Admission Date is the date the event/hospitalization took place. Please complete in the form MM/DD/YYYY with slashes (or an error will appear)



f. Reviewer Initials are your initials (so we can verify who has performed the adjudication). This is especially important for central adjudication:

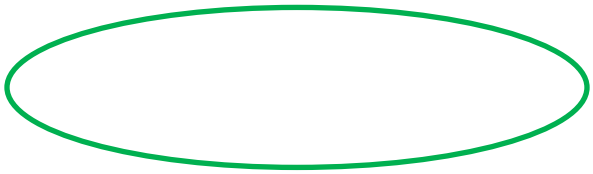


g. EA Tracking number is the corresponding query number that was generated from the ASSESS DMS, which relates to the event being adjudicated. This number should be included with the documentation you receive on the EA_CHK form.

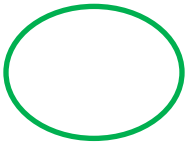


4. To complete each question, simply check next to the 'Yes' or 'No' box and it will submit a check mark as shown here:

5. At the bottom of the Questions is a Comment box for you to write notes or extra information you feel needs to be communicated. This will be stored in the dataset.



6. Note: if you choose to reuse forms after each submission, or you have made a mistake in your form completion, we've added a Clear Form button which erases all your data so far completed (Before and After screen shot):



7. After completion of the form, select the Submit button, where the screen will appear asking for your email and Full Name (selecting the Remember me box will allow you to only enter this once):

8. Select 'Send' and it will ask you whether you want to use a Desktop Email Application (like Outlook) or Internet Mail (like Yahoo or Hotmail). If you plan to always use this method, select the 'Don't show again' box.

9. If your email gets sent automatically, this box will appear as well:

10. A copy of your email will be placed in your Sent folder and will look like the following:

ASSESS AKI

ASsessment,
Serial Evaluation, and
Subsequent Sequelae in AKI
NIH/NIDDK

Biospecimen Manual of Procedures (MOP)

Version:

April 2020

1 BIOSPECIMEN COLLECTION AT THE INPATIENT ADULT VISIT

1.A Overview

Figures 1.1 and 1.2 demonstrate the biospecimen collection related to the hospital or inpatient adult visit. Detailed procedures for collection, urine analysis, processing, storage, and shipping are described in this section.

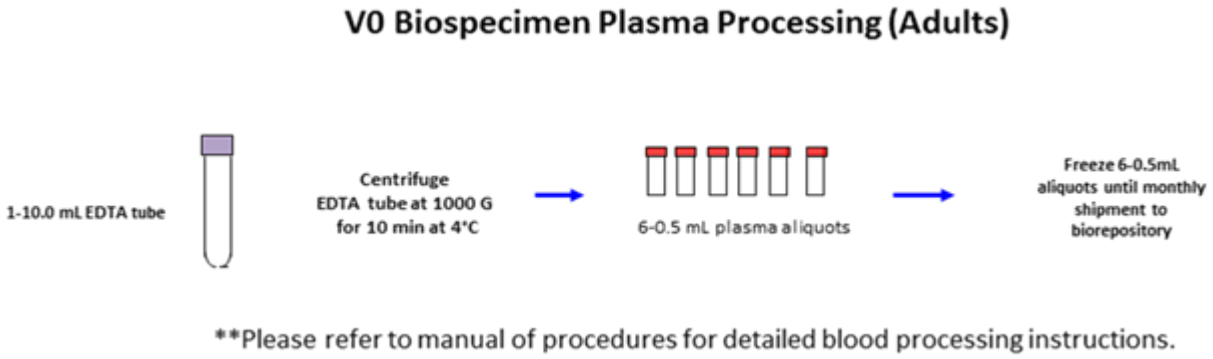


Figure 1.1 V0 Biospecimen Blood Processing (Adults)

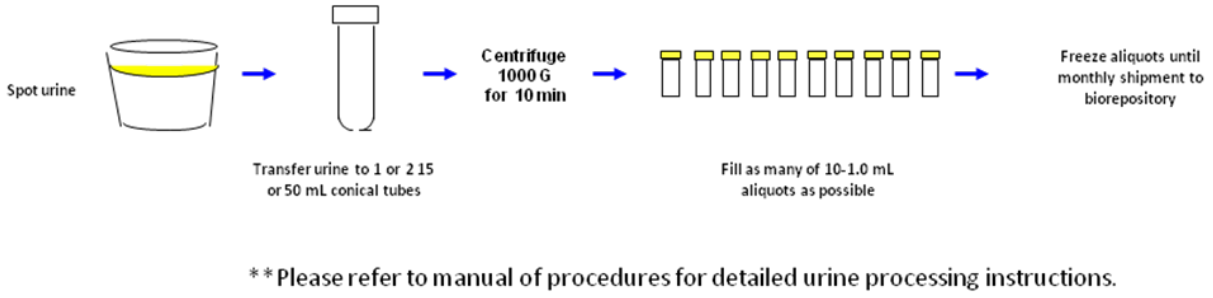


Figure 1.2 V0 Biospecimen Urine Processing (Adults)

It is ideal to collect blood and urine on the same day. It is acceptable to process urine and blood specimens on different days (for example, urine on Day 2 and blood on Day 3), under unusual circumstances when the participant cannot produce a urine specimen or there are problems with blood collection.

*1.B **Blood Collection***

1.B.1 Label Preparation: Vacutainers

- Print the vacutainer labels for each participant to facilitate accurate tracking of collected specimens.
- Pre-label the vacutainers before specimen collection.

1.B.2 Blood Collection

- The inpatient blood draw will be collected in a single lavender top tube supplied by the ASSESS-AKI recruiter. Depending on the study site, this blood draw may be collected by an intensive care unit nurse, study coordinator, or the hospital phlebotomy department.
- In all cases, samples should be spun, aliquoted, and frozen as quickly as possible (see Section 1.D Processing), within six hours of collection. If samples will not be processed within 30 minutes of collection, place samples on ice immediately until the samples are spun, aliquoted, and frozen. For the Inpatient Phase, all aliquots will be sent to the NIDDK Biorepository only, so there is no prioritization scheme for processing or testing.

1.C Urine Collection

In all cases, collected urine samples should be spun and frozen as quickly as possible (see Section 1.3 Processing), within six hours of collection. If samples will not be processed within 30 minutes of collection, place samples on ice immediately until the samples are spun, aliquoted, and frozen at -80°C.

1.C.1 Indwelling Urine Catheter

If participant has an indwelling urinary catheter, urine should be collected from the urine meter or the port on the catheter tubing, not from the large drain bag, within a two-hour window. We recommend clamping the Foley tubing and then using a needleless system to get urine from the tube side port. A nurse caring for the patient or a trained study coordinator may collect this specimen.

1. Place a clamp (e.g., a blue plastic clamp) on the tubing to block the flow of urine into the bag.
2. Wipe the needleless port on the Foley catheter bag with an alcohol wipe and allow it to dry.
3. Access the needleless port with a Luer-lock tip syringe and aspirate back urine.
4. Transfer contents to urine container for transport back to the processing lab.

1.C.2 Clean Catch Void

If participant is spontaneously voiding, ask him/her to do a clean catch void using standard preparation methods described below. Do not take urine from participants who have urostomy bags given the likelihood of contamination. Procedures for collecting a clean catch void are outlined below.

1.C.2.a Urine Collection Items

- Three special towelettes for midstream urine collection. Kaiser site uses a benzalkonium chloride antiseptic towelette.
- 5 oz wide mouthed cup for specimen collection

1.C.2.b Clean Catch Instructions for Males

1. Make sure your bladder is somewhat full.
2. Wash hands thoroughly with soap and water.
3. Retract the foreskin completely, if present.
4. Clean the end of the penis with special towelettes beginning at the urethral opening. Wipe in a circular motion AWAY from the opening.
5. Repeat the above procedure using two successive towelettes.
6. Void into toilet for a few seconds and then stop. Do NOT collect the first amount of urine. Restart urine stream and collect about ½ cup in the sterile container provided.
7. Void the remainder of urine into the toilet.
8. Cap and avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.

9. Bring the container to the study personnel.

1.C.2.c Clean Catch Instructions for Females

"Clean catch" means that the urine sample is not contaminated with any vaginal discharge, menstrual blood, or bacteria.

1. If you have vaginal discharge or are on your period, insert a fresh tampon into the vagina.
2. Wash hands thoroughly with soap and water.
3. Spread labia with 1 hand and hold apart for collection.
4. Use three special towelettes to clean area.
5. Wipe down one side, front to back, with one towelette.
6. Wipe down other side, front to back, with second towelette.
7. Wipe down center, front to back, with last towelette.
8. Void into toilet for a few seconds and then stop. Do NOT collect the first amount of urine. Restart urine stream and collect about ½ cup in the sterile container provided.
9. Void the remainder of urine into the toilet.
10. Cap and avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
11. Bring the container to the study personnel.

1.C.3 Adult Participants Unable to Perform a Clean Catch Void

If participant is spontaneously voiding but unable to perform a clean catch void due to physical constraints (weakness, deconditioning), collect urine as follows.

1. Do not have the participant use cleaning towelettes, as the cleaning agents in the towelettes may interfere with some sensitive bioassays.
2. Have the participant void into a urinal (men) or a clean hat on the toilet or on a commode (men or women).
3. Do not collect urine from a hat that is contaminated with stool.
4. Study personnel should pour a small amount of urine into a labeled specimen cup.
5. Cap the container; avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
6. Record that the urine was not a clean catch specimen in the comment section of the Inpatient Specimen Collection Form (P1_INPT_SPEC).

1.C.4 Urine Sample Prioritization

If the sample is less than 10cc, the sample should be prioritized as follows:

- First 5cc: Aliquots for the NIDDK Biorepository. Enough urine must be available to make 3 x 1mL aliquots for adult participants to enroll in ASSESS-AKI. If between 5 and 10cc is available, make at least 3 x 1mL aliquots.

1.C.5 Urine Analysis

Urine analysis will be performed using the Bayer Clinitek Status Analyzer by the research coordinators. This is mandatory for adult participants.

1.C.5.a If More Than 30cc of Urine Were Collected:

1. Pour approximately 5cc of urine into a 10mL or 15mL conical tube.
2. Dip the test strip into the urine quickly, ensuring all pads are soaked.
3. Place test strip into the analyzer. You will have eight (8) seconds to do this from the time you hit 'Start' on the analyzer.

1.C.5.b If Less Than 30cc of Urine Were Collected:

1 . Use a soft bulb pipette to aspirate 1-2mL of urine.

2 . Quickly pipette 1 drop onto each pad of the stick, ensuring that all pads are soaked.

3 . Place test strip into the analyzer. You will have eight (8) seconds to do this from the time you hit 'Start' on the analyzer.

AFTER DECEMBER 14, 2011, URINE ANALYSIS MICRO IS NOT REQUESTED.

1. Recruiter puts 5 -10mL amount of urine in a second specimen cup. Confirm the volume that is sufficient for your site.
2. Attach a label to the specimen cup.
3. Drop the cup off at the hospital lab.

1.D Processing

1.D.1 Gather Equipment and Supplies

- Centrifuge
- Transfer pipettes
- Aliquot rack
- 14-16 2mL cryogenic vials
- 15mL or 50mL conical tubes for centrifugation
- Balance tubes for centrifugation.
- Waste disposal containers and sharps container
- Cardboard freezer and transport boxes
- Freezer at -80ºC
- Safety: Obtain and utilize necessary protective clothing/equipment for preparing an aliquot of specimens. Such items include but are not limited to lab coats, gloves, protective eyewear, and absorbent pads.

1.D.2 Safety Precautions for Handling Blood and Urine Specimens

- All specimens are handled as potentially infectious for laboratory workers. Transmissions of the infectious agents associated with Hepatitis and HIV via "needle stick" skin punctures have been documented.
- Where feasible, wear disposable plastic gloves when collecting and processing specimens. Alternatively, wash hands thoroughly with disinfectant soap prior to leaving the work area. Skin cuts or abrasions should be covered before starting specimen handling and processing.
- Aliquot/process specimens within a biological safety cabinet.
- Use 0.1% sodium hypochlorite (household bleach) to clean up any spills of blood, plasma, or serum. Use this solution to clean up all laboratory work surfaces at the completion of work activities.
- Dispose of all needles and tubing in puncture-resistant sharps containers for safe disposal.
- Do not perform any pipetting by mouth for any reason.
- Avoid formation of potentially infectious aerosols by careful pipetting and centrifugation.
- All used vacutainers tubes, needles, and blood products are to be placed in spill proof liquid biohazard sharps containers for disposal.

1.D.3 Centrifuge Instructions

1. Separate and sort any specimens that are not centrifuged (i.e. DNA samples or samples to be sent directly to the local lab).
2. Balancing the centrifuge ensures proper performance of the instrument. Determine the amount of sample volume in each tube and find another tube filled to approximately the same level to ensure correct balancing.
3. Use a "balance tube" filled with water to the proper level if there are an uneven number of specimens.
4. After pairing the tubes by their sample volume, place them into the centrifuge using the following guidelines:
    - If the centrifuge contains buckets, position the tubes in the buckets so that the tube and its match are located in opposite buckets (mirror image of each other). Select holes in the opposing buckets that allow for equal weight distribution. See Figure 1.3.
    - Once the centrifuge is loaded with samples, set the speed for 1000 g, room temperature, and time for 10 minutes. Start the centrifuge. At Vanderbilt, Kaiser, and Yale-New Haven, centrifuge is set at 4ºC for processing. At other Yale sites, centrifuge is set at room temperature for processing.
    - Once the centrifuge is stopped, open the centrifuge and remove the specimens.
    - Locate and arrange the specimens by participant to keep each set of specimens and aliquots organized.
    - Aliquot and freeze all biospecimens.
    - If a urine specimen did not pellet properly, go ahead and aliquot and freeze the biospecimen. Do not re-centrifuge. Add this to the comments section (6000) of the Inpatient Specimen Collection Form (P1_INPT_SPEC).
    - If a blood specimen did not pellet properly, respin at 2000 g for 15 minutes, ideally in a refrigerated centrifuge. Add this to the comments section (6000) of the Inpatient Specimen Collection Form (P1_INPT_SPEC).

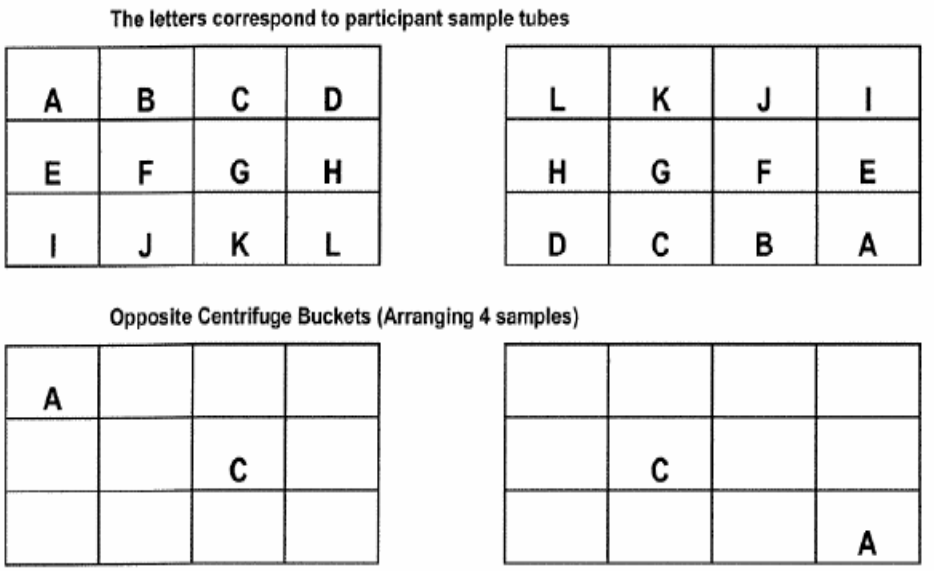


Figure 1.3. Centrifuge Bucket

1.D.4 Create Barcode Labels

The barcode labels will be printed by the individual sites. If additional barcode labels are necessary, allow a minimum three, work-day time window for the DCC to generate and ship labels to the sites to avoid a gap in the ability to conduct visits.

1. The sites will access the Barcodes link on the main website under Direct Module Access.
2. In the Barcode Label Generator screen, the protocol number and center number will populate with the correct information.
3. Select a Print Type of New if this is a new sheet of labels or Re-Print if you are reprinting a label sheet that has already been generated.
4. If Print Type is Re-Print, then the First Urine Sequence needs to be entered to match the first urine sequence on the label sheet (i.e., if AKU0005061 is first urine sequence, then enter 0005061 into the First Urine Sequence field). The first plasma sequence needs to match the first sequence for the EDTA plasma at Visit 0 and will follow the logic that the first urine sequence did. Note: It is imperative that you know the first urine AND first plasma sequence in order to reprint labels, if there is any question about those numbers, simply create a new label sheet and overlabel the samples, rather than possibly duplicate a barcode number.
5. Once the information is entered, select Generate Labels.
6. A .cfm page will appear in Adobe .pdf format where the labels will populate one sheet of labels for one participant at Visit 0.
    - Adobe upgrades can affect the label printing.
    - Sites have reported labels printing offline and therefore labels are wasted.

- Whenever you have upgrades at your site, please print the labels on a blank piece of paper to make sure that alignment is still good.
- If you find that the alignment is off, you can adjust the settings on the print preview screen and print again.
- The most common default on the print preview screen is 'actual size' however this may no longer work when upgrades are distributed for Adobe. Try 'fit' and 'shrink oversized pages'. Either of these settings should allow the labels to align and print correctly on the label sheet.

7. Place the blank label sheet in the laser jet printer face down and print the labels.
8. One label sheet will be printed for each adult participant along with a P1_INPT_SPEC_LOG.

1.D.5 Prepare an Aliquot Sample

- Aliquot samples are necessary any time the original specimen collection tube or container cannot be used for storing and shipping the specimen.
- Verify that the specimens have been properly centrifuged and cells have been clearly separated.
- Use a disposable transfer pipette to transfer the sample from the primary tube to the appropriately labeled secondary tubes, in this case 2mL cryogenic vials.
- When removing plasma or serum using a transfer pipette, be very careful not to disturb the buffy coat (white cell layer) or the serum separator layer.
- Store all aliquots in a plastic rack or cardboard freezer box in an upright position at -80°C immediately. Label the racks or cardboard boxes with permanent marker or an adhesive label that say "ASSESS-AKI Inpatient Biospecimens."

1.D.6 Aliquot Instructions for the Inpatient Visit

- Before aliquoting, affix all barcoded labels lengthwise on the tube for ease of scanning at the sites and the NIDDK Biorepository/central lab/other partner laboratories. It is required to affix the clear adhesive label over the barcode label while overlapping the ends of the clear adhesive label. Make sure that the label does not overlap on top of the barcode because that may interfere with scanning the barcode.
- General Instructions:
  - Using a pipette, transfer the supernatants to the 2mL aliquot tubes provided.
  - Be careful not to disrupt any cellular debris at the bottom of the tube.

1.D.6.a Blood Processing Instructions

1 . Place tubes into the centrifuge and spin for ten minutes at 1000 g in a room temperature centrifuge.

2 . Pipet 0.5mL of plasma into each barcode-labeled 2mL cryovial.

3 . Fill as many of the six (6) available 2mL cryovials as possible. Vials should be filled with exactly 0.5mL. Do not fill a cryovial with less than 0.5mL.

4 . Any leftover blood after aliquoting is completed may be discarded or stored at site.

5 . Scan samples into ASSESS-AKI Biological Sample Tracking system (BST).

6 . Put into a labeled box and place them into the freezer for monthly shipment.

1.D.6.b Urine Instructions

1 . Place the spot urine collection in one 50mL conical vial labeled with the participant's ID.

2 . Centrifuge for 10 minutes at 1000g in a room temperature centrifuge.

3 . Pipet 1mL of supernatant into each barcode-labeled 2mL cryovial.

4 . Fill as many of the 10 available 2mL cryovials as possible. Vials should be filled with exactly 1.0mL. Do not fill a cryovial with less than 1.0mL.

5 . Any leftover urine after aliquoting is completed may be discarded or stored at site.

6 . Affix the duplicate barcode label for each sample on the P1_INPT_SPEC_LOG for each participant by sample type and aliquot number.

7 . Scan samples into ASSESS-AKI Biological Sample Tracking system (BST) using the P1_INPT_SPEC_LOG.

8 . Put into a labeled box and place them into the freezer for monthly shipment.

9 . Any remaining urine can be discarded.

1.E Visit Zero Forms: ADULTS

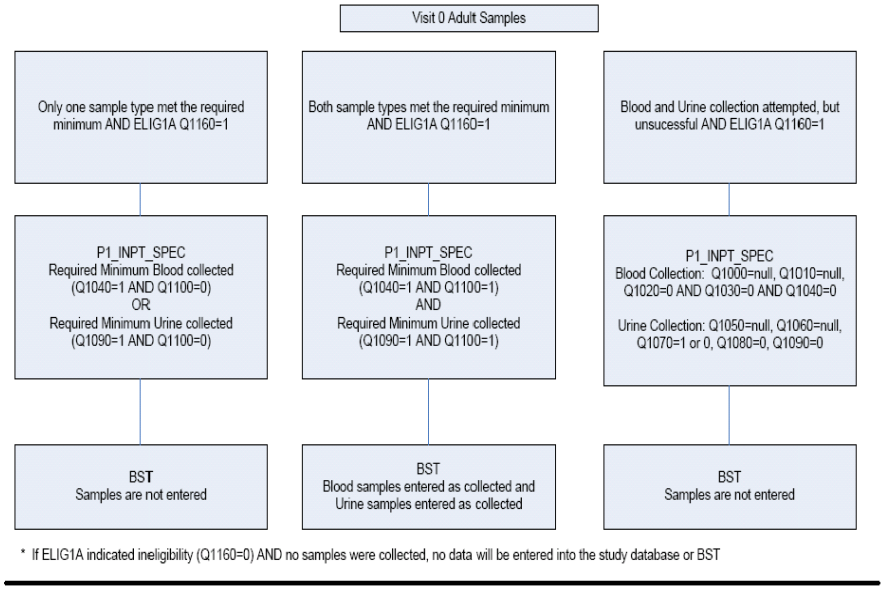
1.E.1 Adult Inpatient Specimen (P1_INPT_SPEC)

- Complete the Visit Date as the current date the Inpatient Specimen Collection (INPT_SPEC) form is completed.
- Q1000. Record the date of the blood draw. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1010. Record the time blood specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1020. Record the amount of blood collected in milliliters. This should be total amount of blood collected, not plasma.
- Q1030. Record the number of 0.5mL aliquots of plasma produced. The ASSESS-AKI goal is 6 (0.5mL aliquots) for adults.
- Q1040. Question regarding the required minimum of 3 aliquots (0.5mL) of plasma being collected for adults.
- Q1050. Record the date of the urine specimen collection. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1060. Record the time urine specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1070. This question is regarding urine collection from a Foley catheter.
- Q1080. Record the number of 1mL aliquots of urine produced. The ASSESS-AKI goal is 10 (1mL aliquots).
- Q1090. Question regarding the required minimum of 3 aliquots (1mL) of urine being collected for adults.
- Q1100. If any of the shaded boxes are chosen in Q1040 or Q1090, the participant is not eligible. If the response to Q1100 is 'NO', complete the ASSESS-AKI Withdrawal (WITHDR) form.
- For more specific details about blood and urine specimen collection requirements, refer to the Biospecimen MOP, Section 1.B and 1.C
- If a Protocol Exception was granted through the DCC, complete the question(s) that the exception was granted for truthfully (i.e. complete the shaded box). Q1100 should be answered 'Yes' to indicate the participant is eligible to proceed and any entry errors that result from the exception should be marked unresolvable. In the unresolvable comment section, indicate that a protocol exception was granted, who granted it, and the justification for the exception.
- Q1110. Record the time plasma samples were frozen using a 24-hour clock. Aliquots should be stored in a -80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.

- Q1120. Record the date the plasma samples were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1130. Record the time urine samples were frozen using a 24-hour clock. Aliquots should be stored in a -80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1140. Record the date the urine samples were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- If blood or urine samples are processed a second time, include a comment in Q6000.
- If processing is completed by someone other than the Coordinator who collected the samples, include the second Coordinator ID in Q6000.
- After the aliquots are produced, enter the aliquot information into the ASSESS-AKI Biological Sample Tracking Module.

1.E.2 Sample Entry Scenarios

- If one sample type indicates ineligibility and the participant is deemed eligible according to the Eligibility Checklist 1A (ELIG1A Q1160 = 1), complete the P1_INPT_SPEC form and DO NOT enter samples into the Biological Sample Tracking (BST) module.
- If a collection was attempted but unsuccessful, and the participant is eligible according to the Eligibility Checklist 1A (ELIG1A Q1160 = 1), complete the P1_INPT_SPEC form and DO NOT enter samples into the Biological Sample Tracking (BST) module.
- If both sample types indicate the participant is eligible and the participant is eligible according to the Eligibility Checklist 1A (ELIG1A Q1160 = 1), complete P1_INPT_SPEC form and enter samples into the Biological Sample Tracking (BST) module.
- If ELIG1A indicated ineligibility (Q1160 = 0) AND no samples were collected, the P1_INPT_SPEC form will not be completed and no data will be entered into the study database or the BST.



1.E.3 P1_INPT_BLOOD_LOG

- At Visit 0, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the site for ease in scanning of the barcode for each sample collected.
- This log will be stored at the site and should not be sent to the DCC.
- This log will be reviewed during ASSESS-AKI site visits.

1.E.4 P1_INPT_URINE_LOG

- At Visit 0, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- This log will be stored at the site and should not be sent to the DCC.
- This log will be reviewed during ASSESS-AKI site visits.

1.F Storage

Store all specimens:

- Immediately freeze all tubes at –80°C after they have been scanned into the ASSESS-AKI Biological Sample Tracking system (BST).
- Store in the upright position until shipped.

1.G Instructions for Scanning the Biosamples into the Biological Sample Tracking (BST) Module

1. Log into the ASSESS website and select the Application link.
2. Select Launch ASSESS AKI Application.
3. Log onto the Biological Sample Tracking module.
4. Select the Enter/Update/Search Sample Tracking.
5. Enter your Participant ID and Visit Number 0 and select the Sample Type.
6. Enter the Collection Date and select 'Execute Query/Insert Samples'.
7. When your barcodes have been scanned, review all of the data on the screen and verify that all the fields are correct.
   - If the default value does not match the volume in the scanned tube, the Sample Volume MUST be changed.
   - Refer to the ASSESS General MOP, Section 10.B.5 for detailed instructions on updating the samples.
8. When the information matches the log and is correct for all fields, select Insert Samples.
9. Next Exit out of the 'Enter/Update/Search' Sample Tracking and go to the 'Build a Shipment' Link.
10. Scan or enter your barcode IDs from the P1 _INPT_BLOOD_LOG and P1 _INPT_URINE_LOG for the biosamples, again you should see these records appear below with the information.
11. Once the records appear on the screen, select the 'Exit Build Shipment' link.
12. Next go into the View Shipments – Mark as Shipped/Print Logs.
13. You should see your build in progress, select the Ship button.
14. Enter a Date Shipment Sent, the tracking number, comments and select Save.
15. Select the Print Log link and save the file to your desktop and/or print and scan a copy. Also select the Create Export File link. Save this file to your desktop.
16. Email the appropriate lab and copy the ASSESS_LAB alias once your shipment is ready and will be sent out that day with the appropriate lab shipping (instructions found below in Section 5).

2 BIOSPECIMEN COLLECTION AT THE OUTPATIENT ADULT VISITS

2.A Overview

Figures 2.1 and 2.2 demonstrate the biospecimen collection related to the 3-month (Visit 3M), 12-month (Visit 12M), and subsequent annual outpatient adult visits (Visits 24M, 36M, 48M, 60M, 72M, and, 84M.). Detailed procedures for collection, urine analysis, processing, storage, and shipping are described in this section.

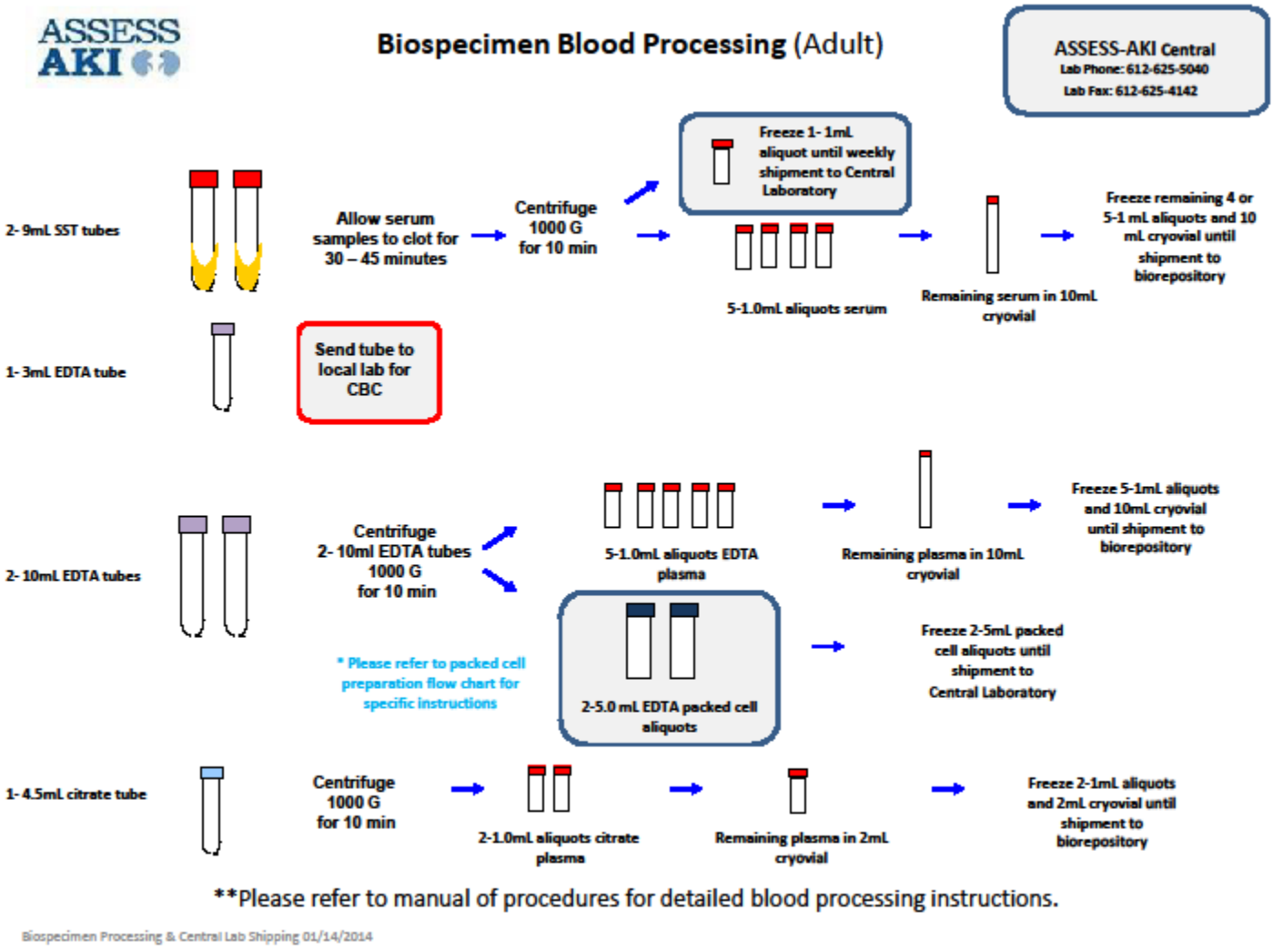


Figure 2.1 Adult Blood Processing

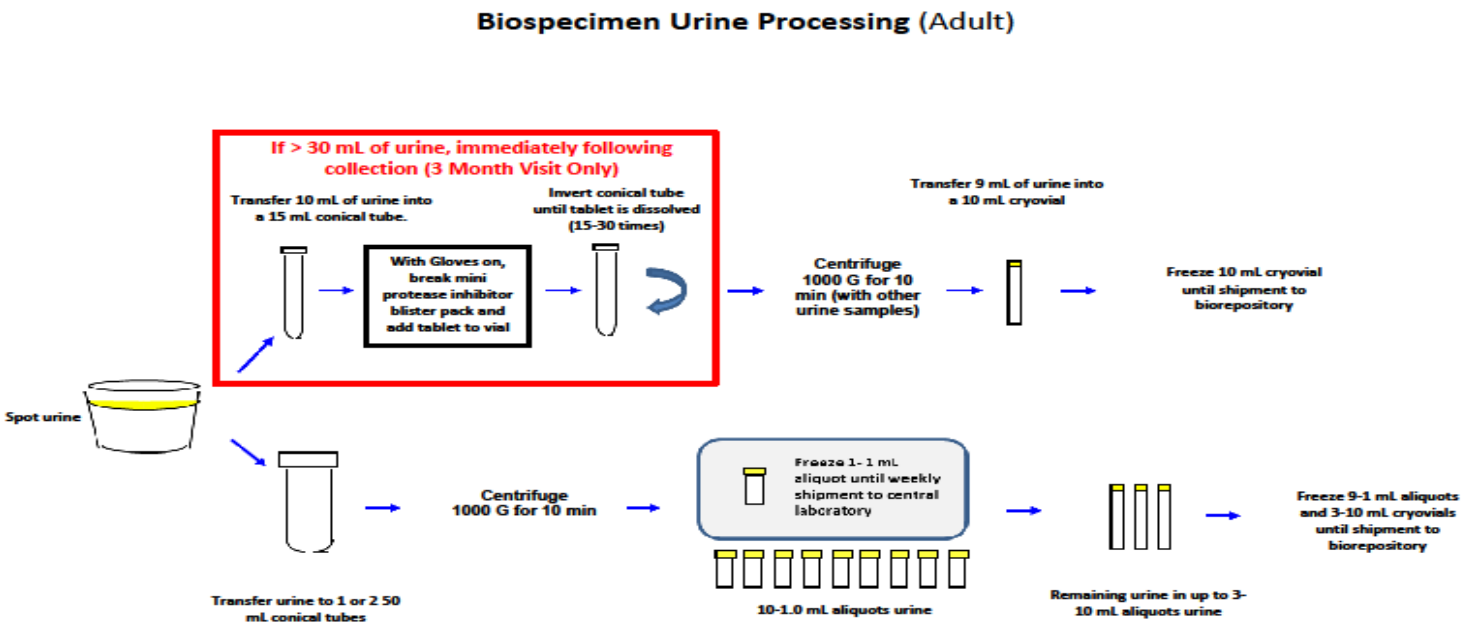


Figure 2.2. Adult Urine Processing

2.B Blood Collection

- This blood draw will be collected by a research coordinator or other qualified staff at all sites. Blood will be drawn into several tubes so that both plasma and serum can be isolated.
- The blood samples should be aliquoted per date and time of collection. See Charts A-D.
- In all cases, samples must be spun, aliquoted, and frozen as quickly as possible (see Section 2.D. Processing), within a target of less than six (6) hours after collection. If samples will not be processed within 30 minutes after collection, samples should be placed on ice immediately after collection until the samples are spun, aliquoted, and frozen at -80ºC. If samples will not be processed within 2.5 hours (from the time that the blood is drawn until processing is started), serum samples are to be processed in the field using battery operated centrifuges, if at all possible and using double serum separator tubes. Plasma and urine tubes will be spun and processed at the Clinical Research Center Laboratory. Refer to the Central Lab supply order form for the double serum separator tubes.

2.B.1 Label Preparation: Vacutainers

- Print the vacutainers labels for each participant to facilitate accurate tracking of collected specimens.
- Pre-label the vacutainers.

2.B.2 Blood Sample Prioritization

Before April 19, 2010, the target blood draw volume was 70mL for Visit 3M when whole blood was sent to the Central Lab for DNA extraction. The priority order of tube collection was as follows:

1. Two 9mL serum separator (red top) tubes for routine visits; two 7.5mL double serum separator tubes for home visits where processing in the field is required
2. One 3mL EDTA (purple top) tube for local lab CBC without differential
3. Two 10mL EDTA (purple top) tubes
4. Two 10mL EDTA (purple top) tubes for DNA
5. One 4.5mL Na citrate (blue top) tube

After April 19, 2010, the target blood draw volume for Visit 3M is 50mL. Frozen packed cells will be sent to the Central Lab for DNA extraction. The DNA will be stored at the Central Lab at -20C. The priority order of tube collection is as follows:

1. Two 9mL serum separator (red top) tubes for routine visits; two 7.5mL double serum separator tubes for home visits where processing in the field is required
2. One 3mL EDTA (purple top) tube for local lab CBC without differential
3. Two 10mL EDTA (purple top) tubes; packed cells for DNA isolation
4. One 4.5mL Na citrate (blue top) tube

The target blood draw volume is 50mL for the subsequent annual adult visits. The priority order of tube collection is as follows:

1. Two 9mL serum separator (red top) tubes for routine visits; two 7.5mL double serum separator tubes for home visits where processing in the field is required
2. One 3mL EDTA purple top tube for local lab CBC without differential
3. Two 10mL EDTA purple top tubes
4. One 4.5mL Na citrate blue top tube

At the Kaiser Permanente Clinical Research Center, blood samples will be drawn in the following priority order (1) serum, (2) Na citrate, (3) EDTA due to hospital policy.

2.B.3 Equipment Preparation

Blood collection tray items for all participants:

- A test tube rack to hold the blood collection tubes which are drawn from each participant; these tubes are described in detail in the next section.
- A plastic vacutainer tube guide
- Three vacutainer Luer slip adaptors to connect the butterfly
- Sterile alcohol swabs
- Gauze sponges
- A tourniquet
- Bandages (Band Aids)
- A stopwatch
- Waste disposal container for sharps

Blood Collection Tray Items for Adults:

- Three sterile, disposable 21 gauge butterfly needles
- Sample aliquot tray items:
  - A rack to hold the aliquot vials, in the same order as the blood collection tubes are drawn
  - Pipetman and pipet tips
  - Soft bulb transfer pipettes to transfer cell pellet
  - Absorbent pads to minimize splashing when opening blood collection tubes
  - 2mL and 10mL aliquot cryovials are provided by the NIDDK Biorepository
  - Red inserts are provided for the clear cap of the blood aliquot cryovials: if the site chooses to use the inserts, the red insert should be applied to all blood aliquot cryovials. Use of the colored inserts is not mandatory.
  - Biohazardous waste disposal container

2.B.4 Blood Collection Preparation

Preparation for specimen collection is done in the following manner in the early morning, prior to arrival of any participants.

1. Check to make sure the blood collection tray is properly equipped. Every item on the checklist must be ready before proceeding.
2. Check that each vacutainer tube is properly labeled with the appropriate participant number.
3. Check that the sample processing tray is properly equipped. Every item on the checklist must be ready and in its proper position.
4. Check that the aliquot processing tray is properly equipped. Every item on the checklist must be ready and in its proper position.
5. Check that each collection tube and aliquot tube is labeled with the appropriate participant identification number.
6. Check that the centrifuge is working properly.
7. Check the freezer temperature (-80ºC).

Phlebotomy Room:

1. The blood draw should take place in an isolated room or participants should be separated by room dividers.
2. The room must be equipped with all of the necessary blood specimen supplies.
3. A separate counter or worktable must be equipped with all of the materials and vials that are used in the blood handling and processing.
4. The centrifuge and freezer should be nearby.

2.B.5 Participant Preparation

- Anticipate at least 15 minutes per participant.
- At participant arrival:
  - Check that each blood collection tube is labeled with the participant's name/medical record number or participant ID.
  - Check that the aliquot tubes are prepared and labeled correctly.
- Participant Preparation:
  - Informed consent must be obtained by the trained staff member before drawing blood. This procedure is followed to ensure that the participants understand the purpose of blood drawing and the possible complications of venipuncture. A standard informed consent has been prepared for this study at each participating site. With regard to laboratory procedures, the consent statement informs study participants that there is a small risk of bruising at the spot on the area where the blood is taken. The consent statement also informs study participants that a copy of

the test results is sent to their physician, and that they will be contacted if clinically important tests are abnormal.

- The participant is asked whether he/she has a bleeding disorder before the blood is drawn. If such a disorder is present, ask the participant whether he/she has had blood drawn previously and if so, whether he/she had any problems with excessive bleeding or bruising at the venipuncture site. If the participant has a history of venipuncture problems, the participant should be sampled only if approved by the physician.
- Ask the participant if he/she or his/her doctor have a preference as to which vein to use to determine whether or not he/she has been told to protect a particular vein or particular upper extremity.
- If not, it is recommended that the medial-most antecubital vein in the dominant arm is used, assuming that the non-dominant arm will be the access arm of choice if the subject goes on to need dialysis, and that the medial most antecubital vein is not likely to be the draining cephalic vein.
- The venipuncture is performed with a 21 gauge butterfly needle with 12 inches of plastic tubing between the venipuncture site and the blood collection tubes. The butterfly has a small, walled needle which minimizes trauma to the skin and vein. The use of 12 inches of tubing allows tubes to be changed without any movement of the needle in the vein. If the participant is concerned about the venipuncture, he/she may be reassured to know such care is taken.
- The participant should be given enough time to feel comfortable both before and after the blood collection. In many cases the most memorable part of the experience will be the contact with the technologist who draws the blood and his/her general attitude and competence.

- Handling participants who are extremely apprehensive about having blood drawn:
  - Do not under any circumstances force the participant to have blood drawn.
  - If the participant is nervous or excited, the technologist should briefly describe the procedure:
    - "I am going to be drawing about five (5) tablespoons of blood. This blood will be used in tests for kidney function and other research analyses. We hope to be able to use the results of these tests to predict who might have a greater risk of kidney and heart disease."
  - Explain to the participant that the blood drawing is designed to be as nearly painless as possible. It is sometimes best to let the participant go on with another part of the visit.
  - Have the participant relax in the blood drawing chair just so the phlebotomist can check the veins in the participant's arms, without actually drawing blood.
  - If the participant has "good veins" the phlebotomist can reassuringly say, "Oh, you have good veins; there should be no problem."

2.B.6 Venipuncture Procedure

1. Preparation.
   - Remove all extra clothing and have the participant sit upright with the sleeves rolled up to expose the antecubital fossa (elbow).

- A tourniquet is used to increase venous filling. It makes the veins more prominent and easier to enter.

2. Precautions When Using a Tourniquet:
   - The tourniquet should be on the arm for the shortest time possible.
   - Never leave the tourniquet on for longer than two (2) minutes. To do so may result in hemoconcentration or a variation of blood test values.
   - If a tourniquet must be applied for the preliminary vein selection, it should be released and reapplied after a wait of two minutes.
   - If the participant has a skin problem, put the tourniquet over the participant's shirt or use a piece of gauze or paper tissue so as not to pinch the skin.
   - Wrap the tourniquet around the arm 3 to 4 inches (7.5 to 10.0 cm) above the venipuncture site.
   - Tuck the end of the tourniquet under the last round. If a Velcro tourniquet is used, adhere the ends to each other.
3. Identify the vein:
   - Palpate and trace the path of veins several times with the index finger. Thrombosed veins lack resilience, feel cord-like, and roll easily.
   - If superficial veins are not readily apparent, have the participant close his or her fist.
   - Lowering the extremity over the arm of the chair will allow the veins to fill to capacity.
   - Identify the best available vein.
4. Cleanse the venipuncture site.
   - Remove alcohol pad from its sterile package.
   - Cleanse the vein site with the alcohol pad using a circular motion from the center to the periphery.
   - Allow the area to dry to prevent possible hemolysis of the specimen and a burning sensation to the participant when the venipuncture is performed.
5. Assemble the butterfly-vacutainer set.
   - Attach the Luer adaptor to the vacutainer holder.
   - Attach the Luer end of the butterfly needle set to the Luer adaptor.
6. Perform venipuncture.
   - Grasp the participant's arm firmly, using your thumb to draw the skin taut. This anchors the vein. The thumb should be 1 or 2 inches (2.3 or 5.0 cm) below the venipuncture site.
   - With the needle bevel upward, enter the vein in a smooth continuous motion.
   - Make sure the participant's arm is in a flat or downward position while maintaining the tube below the site when the needle is in the vein. It may be helpful to have the participant make a fist with the opposite hand and place it under the elbow for support.
   - Grasp the flange of the needle holder and push the tube forward until the butt end of the needle punctures the stopper, exposing the full lumen of the needle.

- Start a timer to measure the flow rate of blood into the first blood collection tube. If the flow rate in the tube is so slow that blood does not fill the first collection tube within 50 seconds, stop the blood collection and repeat on the other arm. If blood is flowing freely, the butterfly tubing can be anchored to the participant's arm using medical tape for the duration of the draw.
- Remove the tourniquet after blood is flowing into the second tube.
- Keep a constant, slight forward pressure (in the direction of the needle) on the end of the tube. This prevents release of the shutoff valve and stopping of blood flow. Do not vary pressure nor reintroduce pressure after completion of the draw.
- Fill each vacutainer tube as completely as possible; i.e., until the vacuum is exhausted and blood flow ceases. If a vacutainer tube fills only partially, remove the vacutainer and attach another one without removing needle from vein.
- When the blood flow ceases, remove the tube from the holder. The shutoff valve recovers the point, stopping blood flow until the next tube is inserted.
- EDTA tubes and Na Citrate tubes should be gently mixed by inverting immediately after each tube is filled and removed from the butterfly setup.
- If it is not possible to collect all of the desired tubes, follow the requested order and fill each tube as completely as possible.

7. Prevent blood mixing during venipuncture.
   - Only invert tubes containing anticoagulant such as EDTA (purple top) and Na Citrate (blue top) collection tubes.
   - DO NOT SHAKE TUBES!!
   - To invert tubes, hold the tube horizontal to the floor.
   - Slowly tip the butt end down while watching the air bubble rise to the stopper (1st inversion).
   - When the bubble reaches the stopper, the tube should be at approximately a 22 degree angle to the floor.
   - Next lower the stopper while watching the bubble float to the butt end. Again the tube should be at a 22 degree angle to the floor (2nd inversion).
   - Lower the butt end again. This is the third inversion.
   - Invert each tube eight times. Eight inversions should take 13-15 seconds.
   - Proceed to Section 2.D Processing
8. If a blood sample is not forthcoming, the following manipulations may be helpful:
   - If there is a sucking sound, the tube has lost its vacuum. Replace with a new tube.
   - If no blood appears, move the needle slightly in hope of entering vein. Do Not Probe. If not successful, release tourniquet and remove needle. A second attempt can be made on the other arm.
   - The same technician should not attempt a venipuncture more than twice.
   - To remove the needle, lightly place clean gauze over venipuncture site. Remove the needle quickly and immediately apply pressure to the site with a gauze pad.

- Discard needle with its cap into a sharps container.

9. Bandage the arm.
   - Under normal conditions:
     - Slip the gauze pad down over the site, continuing mild pressure.
     - Apply an adhesive or gauze bandage over the venipuncture site after making sure blood flow has stopped.
   - If the participant continues to bleed:
     - Apply pressure to the site with a gauze pad. Keep the arm elevated until the bleeding stops.
     - Wrap the gauze bandage tightly around the arm over the pad.
     - Tell the participant to leave the bandage on for at least 15 minutes.
10. Precautions – If a participant feels faint or looks faint following the blood draw:
    - Have the person remain in the chair, if necessary have him/her sit with head between knees.
    - Take an ampule of smelling salts, crush it, and wave it under person's nose for a few seconds.
    - Provide the person with a basin if he/she feels nauseous.
    - Have the person stay reclined until their color returns and he/she feels better.
    - Place a cold wet cloth on the back of the person's neck.
    - If the person faints, use smelling salts to revive.
    - If the person continues to feel sick, take a blood pressure and pulse reading. Contact a medical staff member, who will advise you on further action.

2.C Urine Collection

- In all cases, the freshest urine should be collected.
- The urine samples should be aliquoted per date and time of collection. See Charts A-D.
- Urine should be collected from a single void and not pooled from several voids, even if the desired 50mL volume is not achieved. If the first void is less than 30cc, place the specimen on ice and hold for up to two hours. In the meantime, offer the participant a glass of water; avoid an acute fluid load (> 24 ounces in 2 hours). Ask them to produce a second specimen within 2 hours. Process the LARGER of the two specimens and discard the lower-volume specimen.
- In all cases, samples must be spun and frozen as quickly as possible (see Section 2.D Processing), within six (6) hours of collection. If samples will not be processed within 30 minutes of collection, place samples on ice immediately until the samples are spun, aliquoted, and frozen at 80°C.
- At Visit 3M, if more than 30cc is available, one aliquot of urine will have protease inhibitors added as soon as possible after the urine is collected. The remaining urine will be split for processing and for urinalysis using the Bayer Clinitek Status Analyzer. At all other adult visits, urine will be split for processing and for urinalysis only.
- The only time that a urine sample may be collected by a participant at home and the participant may bring the urine sample to the visit is when the visit is an in-clinic visit, the urine was collected by straight catheter, and the urine was refrigerated or on ice/ice pack. All three conditions must be met. Indwelling Foley catheters are not included. This does not pertain to home visits. The Coordinator should email the DCC Scientific Coordinator and copy ASSESS_DM to request a protocol exception and include the participant ID and confirm in writing that 1) visit was an in-clinic visit, 2) urine was collected by straight catheter, and 3) urine sample was refrigerated, on ice, or on ice pack. The site coordinator should make a note of this in the Comments section of the urine collection forms.

2.C.1 Clean Catch Void

Participants should do a clean catch void, if at all possible. Do not take urine from participants who have urostomy bags. Procedures for collecting a clean catch void are outlined below.

2.C.1.a Urine Collection Items

- Three special towelettes for midstream urine collection. Kaiser site uses a benzalkonium chloride antiseptic towelette.
- 5 oz wide mouthed cup for specimen collection

2.C.1.b Clean Catch Instructions for Males

1. Make sure your bladder is somewhat full.
2. Wash hands thoroughly with soap and water.
3. Retract the foreskin completely, if present.

4. Clean the end of the penis with special towelettes beginning at the urethral opening. Wipe in a circular motion AWAY from the opening.
5. Repeat the above procedure using two successive towelettes.
6. Void into toilet for a few seconds and then stop. Do NOT collect the first amount of urine. Restart urine stream and collect about ½ cup in the sterile container provided.
7. Void the remainder of urine into the toilet.
8. Cap and avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
9. Bring the container to the study personnel.

2.C.1.c Clean Catch Instructions for Females

"Clean catch" means that the urine sample is not contaminated with any vaginal discharge, menstrual blood, or bacteria.

1. If you have vaginal discharge or are on your period, insert a fresh tampon into the vagina.
2. Wash hands thoroughly with soap and water.
3. Spread labia with 1 hand and hold apart for collection.
4. Use three special towelettes to clean area.
5. Wipe down one side, front to back, with one towelette.
6. Wipe down other side, front to back, with second towelette.
7. Wipe down center, front to back, with last towelette.
8. Void into toilet for a few seconds and then stop. Do NOT collect the first amount of urine. Restart urine stream and collect about ½ cup in the sterile container provided.
9. Void the remainder of urine into the toilet.
10. Cap and avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
11. Bring the container to the study personnel.

2.C.2 Participants Unable to Perform a Clean Catch Void

If participant is spontaneously voiding but unable to perform a clean catch void due to physical constraints (weakness, deconditioning), collect urine as follows.

1. Do not have the participant use cleaning towelettes, as the cleaning agents in the towelettes may interfere with some sensitive bioassays.
2. Have the participant void into a urinal (men) or a clean hat on the toilet or on a commode (men or women).
3. Do not collect urine from a hat that is contaminated with stool.
4. Study personnel should pour a small amount of urine into a labeled specimen cup.

5. Cap the container; avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
6. Record that the urine was not a clean catch specimen in the comment section of the Adult Outpatient V3M Specimen Collection: Urine (P1_V3M_COLLECT_UA) form at V3M and Adult Outpatient Yearly Specimen Collection: Urine (P1_OUTPT_COLLECT_UA) form at the annual visits.

2.C.3 Urine Sample Prioritization

If the sample is less than 10 cc, the sample should be prioritized as follows:

- First 5 cc: Aliquots for the Central Lab and NIDDK Biorepository. Urine should be aliquoted as 1mL aliquots.
- If between 5cc and 10cc is available, make at least 5 x 1mL aliquots. Perform urinalysis with Bayer Clinitek Status Analyzer as below.
- At the Visit 3M, if more than 30cc is available, a 10mL aliquot should be saved with protease inhibitors per the protocol below.

2.C.4 Addition of Protease Inhibitor Tablets

1. Immediately after the sample is received from the participant, the study coordinator should transfer 10mL of urine into a separate 15mL conical tube.
2. With gloves on, break Roche Mini Protease Inhibitor with EDTA blister pack. Add tablet to tube.
3. Invert to mix until tablet is dissolved (15-30 times). Protease inhibitor tablets should be added before the specimen is placed on ice because the tablet takes a long time (many inversions) to dissolve in a 4°C sample.
4. Process and spin with other samples (see Section 2.D. Processing). As with other samples, place on ice if it will not be processed within 30 minutes.

2.C.5 Urine Analysis

Urine analysis will be performed using the Bayer Clinitek Status Analyzer by the research coordinators. This is mandatory for adult participants in whom a clean catch void was obtained. For home visits, urine analysis will be done at the Clinical Research Center, not in the participants' home.

2.C.5.a If More Than 30cc of Urine Were Collected:

1. Pour approximately 5cc of urine into a 10mL or 15mL conical tube.
2. Dip the test strip into the urine quickly, ensuring all pads are soaked.
3. Place test strip into analyzer. You will have eight (8) seconds to do this from the time you hit 'Start' on the analyzer.

2.C.5.b If Less Than 30cc of Urine Were Collected:

1. Use a soft bulb pipette to aspirate up 1-2mL of urine.

2. Quickly pipette one drop onto each pad of the stick, ensuring that all pads are soaked.
3. Place test strip into analyzer. You will have eight (8) seconds to do this from the time you hit 'Start' on the analyzer.

*2.D **Processing***

The processing of specimens should be completed within six (6) hours of collection and preferably within 2.5 hours, if possible. Blood and urine biospecimens should be stored on ice or refrigerated until processed. Follow the instructions below to centrifuge and aliquot the blood and urine specimens for the inpatient visit. If samples will not be processed within 2.5 hours (from the time that the blood is drawn until processing is started), serum samples are to be processed in the field using battery operated centrifuges. Plasma and urine tubes will be spun and processed at the Clinical Center Laboratory.

2.D.1 Gather Equipment and Supplies

- Centrifuge
- Transfer pipettes
- Aliquot rack
- 24 2mL cryovials (10 for urine, 14 for blood) and six (6) 10mL cryovials (four (4) for urine, two (2) for blood) for complete collection; at V3M, two (2) 5mL cryovials are needed for frozen packed cell collection
- Cap inserts (red for blood aliquots, yellow for urine aliquots) are provided for the Clinical Research center. Use of the colored inserts is not mandatory.
- 15mL or 50mL conical tubes for centrifugation
- Balance tubes for centrifugation.
- Waste disposal containers and sharps container
- Cardboard freezer and transport boxes
- Freezer at -80ºC
- Safety: Obtain and utilize necessary protective clothing/equipment for preparing an aliquot of specimens. Such items include but are not limited to lab coats, gloves, protective eyewear, and absorbent pads.

2.D.2 Safety Precautions for Handling Blood and Urine Specimens

- All specimens are handled as potentially infectious for laboratory workers. Transmissions of the infectious agents associated with Hepatitis and HIV via “needle stick” skin punctures have been documented.
- Where feasible, wear disposable plastic gloves when collecting and processing specimens. Alternatively, wash hands thoroughly with disinfectant soap prior to leaving the work area. Skin cuts or abrasions should be covered.
- Aliquot/process specimens within a biological safety cabinet.
- Use 0.1% sodium hypochlorite (household bleach) to clean up any spills of blood, plasma, or serum. Use this solution to clean up all laboratory work surfaces at the completion of work activities.
- Dispose of all needles and tubing in puncture-resistant sharps containers for safe disposal.

- Do not perform any pipetting by mouth for any reason.
- Avoid formation of potentially infectious aerosols by careful pipetting and centrifugation.
- All used Vacutainers tubes, needles, and blood products are to be placed in spill proof liquid biohazard sharps containers for disposal.

2.D.3 Centrifuge Instructions

1. Separate and sort any specimens that are not centrifuged (i.e. DNA samples or samples to be sent directly to the local lab).
2. Allow serum samples to clot for at least 30 minutes prior to processing.
3. Balancing the centrifuge ensures proper performance of the instrument. Determine the amount of sample volume, in each tube and find another tube filled to approximately the same level to ensure correct balancing.
4. Use a "balance tube" filled with water to the proper level if there are an uneven number of specimens.
5. After pairing the tubes by their sample volume, place them into the centrifuge using the following guidelines:
    - If the centrifuge contains buckets, position the tubes in the buckets so that the tube and its match are located in opposite buckets (mirror image of each other). Select holes in the opposing buckets that allow for equal weight distribution. See Figure 2.3.
    - Once the centrifuge is loaded with samples, set the speed for 1000 g, and time for 10 minutes. Start the centrifuge. At Vanderbilt, Kaiser and Yale-New Haven, centrifuge is set at 4°C for processing. At other Yale sites, centrifuge is set at room temperature for processing.
    - Once the centrifuge is stopped, open the centrifuge and remove the specimens.
    - Locate and arrange the specimens by participant to keep each set of specimens and aliquots organized.
    - Aliquot and freeze all biospecimens.
    - If a urine specimen did not pellet properly, go ahead and aliquot and freeze the biospecimen. Do not re-centrifuge. Add this to the comments section (6000) of the V3M/Outpatient Specimen Collection Forms (P1_V3M_COLLECT_UA, P1_OUTPT_COLLECT_UA).
    - If a blood specimen did not pellet properly, respin at 2000 g for 15 minutes, ideally in a refrigerated centrifuge. Add this to the comments section (6000) of the V3M/Outpatient Specimen Collection Forms (P1_V3M_COLLECT_BLD, P1_OUTPT_COLLECT_BLD).

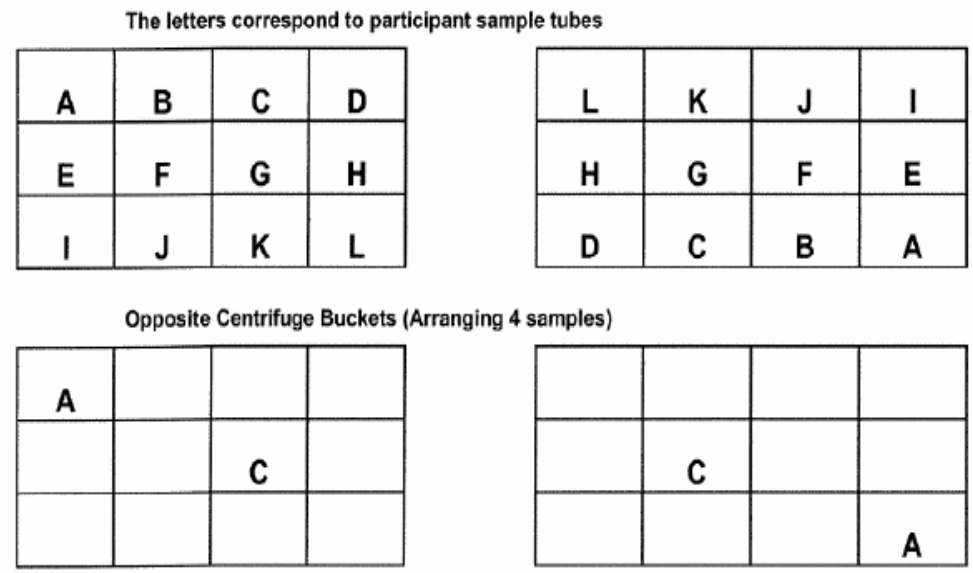


Figure 2.3. Centrifuge Bucket

2.D.4 Create Barcode Labels

The barcode labels will be printed by the individual sites. If additional barcode labels are necessary or if there are problems printing labels at the site, allow a minimum five work-day window for the DCC to generate and ship labels to the sites.

1. The sites will access the Barcodes link on the main website under Direct Module Access or within the specified protocol (1- adults).
2. In the Barcode Label Generator screen, the protocol number and center number will populate with the correct information.
3. Select a Print Type of New if this is a new sheet of labels or Re-Print if you are reprinting a label sheet that has already been generated.
4. Select a Print Duplicates with option 'Yes' if the user wants a duplicate page to be printed for the URINE_LOG and BLOOD_LOG forms.
5. Once the information is entered, select Generate Labels.
6. A .cfm page will appear in Adobe .pdf format where the labels will populate one sheet of labels for one participant at the Visit.
    - Adobe upgrades can affect the label printing.
    - Sites have reported labels printing offline and therefore labels are wasted.
    - Whenever you have upgrades at your site, please print the labels on a blank piece of paper to make sure that alignment is still good.

- If you find that the alignment is off, you can adjust the settings on the print preview screen and print again.
- The most common default on the print preview screen is 'actual size' however this may no longer work when upgrades are distributed for Adobe. Try 'fit' and 'shrink oversized pages'. Either of these settings should allow the labels to align and print correctly on the label sheet.

7. Place the blank label sheet in the laser jet printer face down and print the labels.
8. One label sheet will be printed for each adult participant along with a P1_V3M_URINE_LOG, P1_V3M_BLOOD_LOG, P1_VXXM_URINE_LOG, and P1_VXXM_BLOOD_LOG.

2.D.5 Prepare an Aliquot Sample

- Aliquot samples are necessary any time the original specimen collection tube or container cannot be used for storing the specimen.
- Verify that the specimens have been properly centrifuged and cells have been clearly separated.
- Use a disposable transfer pipette to transfer the sample from the primary tube to the appropriately labeled secondary tubes, in this case 2mL cryovials.
- When removing plasma or serum using a transfer pipette, be very careful not to disturb the buffy coat (white cell layer) or the serum separator layer.
- When removing urine using a transfer pipette, do not transfer the sediment to the appropriately labeled secondary tube(s).
- Store all aliquots in a plastic rack or cardboard freezer box in an upright position at -80°C immediately. Label the racks or cardboard boxes with permanent marker or an adhesive label that say "ASSESS-AKI Outpatient Biospecimens."

2.D.6 Aliquot Instructions for Outpatient Adult Visits

- Before aliquoting, affix all barcoded labels lengthwise on the tube for ease of scanning at the sites and the NIDDK Biorepository/central lab/other partner laboratories. It is required to affix the clear adhesive label over the barcode label while overlapping the ends of the clear adhesive label. Make sure that the label does not overlap on top of the barcode because that may interfere with scanning the barcode.
- General Instructions:
- Red inserts should be used for the cap of the blood specimen aliquots and yellow inserts for the caps of the urine specimen aliquots.
- Using a pipette, transfer the supernatants to the 2mL aliquot tubes provided.
- Be careful not to disrupt any cellular debris at the bottom of the tube.
- The 3mL EDTA purple top tube is not aliquoted. It is sent to the Clinical Research Center local laboratory for CBC measurements.

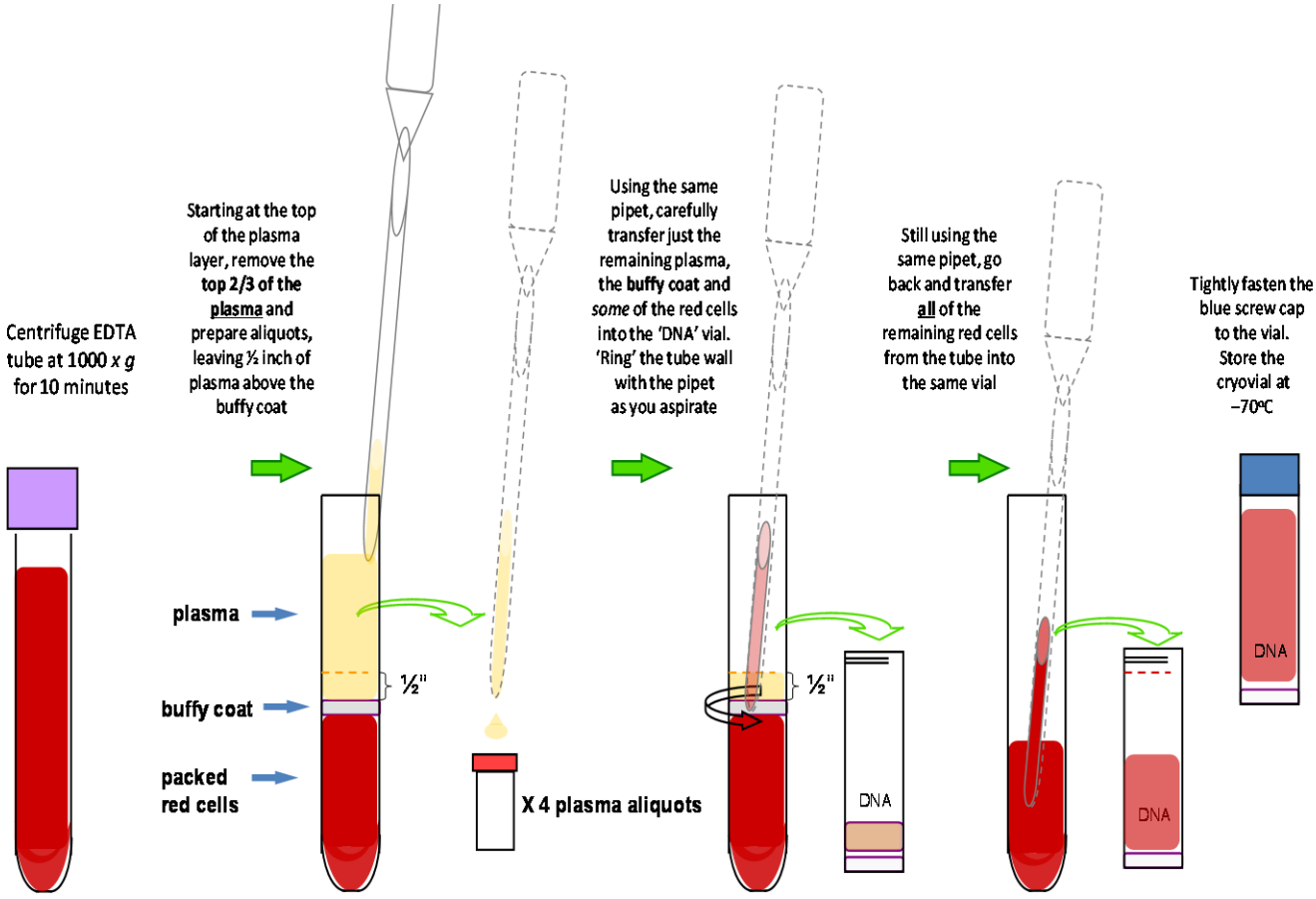
2.D.6.a Serum Separator Tube (Red Top) Instructions

1. Allow tubes to clot upright for at least 30 minutes prior to processing at room temperature.
2. Place tubes into the centrifuge and spin for ten minutes at 1000 g.
3. Pipet 1mL of serum into each barcode-labeled 2mL cryovial.
4. Fill as many of the five (5) available cryovials as possible. Vials should be filled with exactly 1mL. Do not fill a cryovial with less than 1mL.
5. One aliquot should be sent to the Central Lab. All other serum aliquots will be shipped to the NIDDK Biorepository.
6. If there is leftover serum after the 5 x 1mL aliquots are filled, the remaining serum should be transferred to a 10mL cryovial.
7. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST).
8. Put the cryovials for the Central Lab into a labeled box and place them into the freezer for weekly shipment.
9. Put the cryovials for the NIDDK Biorepository into a labeled box and place them into the freezer for monthly shipment.

2.D.6.b EDTA Plasma (Purple Top) Instructions

1. Place tubes into the centrifuge and spin for ten minutes at 1000 g as soon as possible after collection.
2. Pipet 1mL of plasma into each barcode-labeled 2mL cryovial. Leave ½ inch of plasma above the packed cells. Fill as many of the 5 cryovials as possible. Vials should be filled with exactly 1mL. Do not fill a cryovial with less than 1mL.
3. If there is leftover plasma after the 5 x 1mL aliquots are filled, the remaining plasma should be transferred to a 10mL cryovial.
4. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST).
5. Put the cryovials for the NIDDK Biorepository into a labeled box and place them into the freezer for monthly shipment.

2.D.6.c Packed Cell Pellet for DNA Extraction:



Processing the EDTA tube collected for DNA isolation:

Centrifuge the EDTA tube promptly at 1000 x *g* for 10 minutes. Being careful not to disturb the buffy coat and packed red cell layers, use a plastic transfer pipet to remove the top 2/3 of the clear plasma supernatant and prepare plasma aliquots. Aspirate slowly starting at the top of the plasma. The pipet tip should not get any closer than one-half inch from the buffy coat. (Priority should be given to obtain adequate plasma volume.) It is important to withdraw only the plasma and *none* of the buffy coat (containing white cells and platelets) that forms at the cell-plasma interface following centrifugation. Leave a ½-inch layer of plasma above the buffy coat-red blood cell layers whenever possible.

Using the same plastic transfer pipet, slowly aspirate the remaining ½" layer of plasma, the buffy coat and *some* of the red cells from the tube. Take care not to aspirate the buffy coat into the bulb of the pipet! 'Ring' the tube with the pipet by carefully aspirating along the wall at the buffy coat layer to ensure maximum transfer. Dispense into the 5-mL packed cell aliquot vial. Still using the same pipet, go back and transfer all of the remaining packed red cells from the tube into the same 5-mL'DNA' vial. This step will ensure that all of the buffy coat is adequately rinsed from the pipet. Tightly fasten the blue screw cap on this vial and place it in the –70°C freezer.

Figure 2.4. Packed Cell Preparation

At Visit 3M only, transfer the cell pellet to a labeled cryovial for DNA extraction. To collect the cell pellet:

1. Using a soft bulb plastic transfer pipette, slowly aspirate the remaining ½" layer of plasma, the buffy coat and *some* of the red cells from the tube. Take care not to aspirate the buffy coat into the bulb of the pipette! 'Ring' the tube with the pipette by carefully aspirating along the wall at the buffy coat layer to ensure maximum transfer.
2. Dispense into the 5mL packed cell aliquot vial.
3. Still using the same pipette, go back and transfer all of the remaining packed red cells from the tube into the same 5mL'DNA' vial. This step will ensure that the entire buffy coat is adequately rinsed from the pipette.
4. Do not transfer just the buffy coat, since there are some white blood cells in the red cell pellet and transferring the entire cell pellet increase the yield.
5. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST).
6. Put the cryovials into a labeled box and place them into the freezer for weekly shipment to the Central Lab.

2.D.6.d Citrate Plasma (Blue Top) Instructions

1. Place tubes into the centrifuge and spin for ten minutes at 1000 g as soon as possible after collection.
2. Pipet 1mL of plasma into each barcode-labeled 2mL cryovial.
3. Fill as many of the 2mL cryovials as possible. Vials should be filled with exactly 1mL. Do not fill a cryovial with less than 1mL.
4. If there is leftover plasma after the 2 x 1mL aliquots are filled, transfer the remaining plasma to a 2mL cryovial.
5. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST).
6. Put the cryovials for the NIDDK Biorepository into a labeled box and place them into the freezer for monthly shipment.

2.D.6.e Collection Logs for Blood Aliquots

1. Affix the duplicate barcode label for each sample on the P1_V3M_BLOOD_LOG or P1_VXXM_BLOOD_LOG for each participant by sample type and aliquot number.
2. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST) using the P1_V3M_BLOOD_LOG or P1_VXXM_BLOOD_LOG.

2.D.6.f Urine Instructions

1. If this is a V3M specimen and more than 30mL is collected, 10mL should be processed with protease inhibitors (see section 2.B.2.).
2. Place the spot urine collection in one or two 50mL conical vial labeled with the participant's ID, depending on the sample volume.

3. Centrifuge for 10 minutes at 1000 g.
4. Pipet 1mL of supernatant into each barcode-labeled 2mL cryovial.
5. Fill as many of the 10 cryovials as possible. Vials should be filled with exactly 1.0mL. Do not fill a cryovial with less than 1.0mL.
6. One aliquot should be sent to the Central Lab. All other urine aliquots will be shipped to the NIDDK Biorepository.
7. If there is leftover urine after the 10 x 1mL aliquots are filled, the remaining urine should be transferred to 10mL cryovials. Fill up to three 10mL cryovials at the 3-month adult visit, or four 10mL cryovials at the 12-month adult visit.
8. Any leftover urine after aliquoting is completed may be discarded or stored at the Clinical Research Center.
9. Put the cryovials for the Central Lab into a labeled box and place them into the freezer for weekly shipment.
10. Put the cryovials for the NIDDK Biorepository into a labeled box and place them into the freezer for monthly shipment.

2.D.6.g Collection Logs for Urine Aliquots

1. Affix the duplicate barcode label for each sample on the P1_V3M_URINE_LOG or, P1_VXXM_URINE_LOG for each participant by sample type and aliquot number.
2. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST) using the P1_V3M_URINE_LOG or P1_VXXM_URINE_LOG.

2.E Visit 3M Forms: ADULTS

2.E.1 P1_V3M_COLLECT_BLD

- Complete the Visit Date as the current date the Adult Outpatient V3M Specimen Collection: Blood (P1_V3M_COLLECT_BLD) form is completed.
- Q1000. This question is completed for home visits only to indicate if extra time will be allowed between collection and processing.
- Q1010. Record the date of the blood draw. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1020. Record the time blood specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1030. Was the minimum amount (10mL) of blood collected?
  - IF NO, reschedule another collection within 48 hours of these collections and complete the Outpatient V3M Specimen 2+ Collection:Blood (P1_V3M_COLLECT_BLD_2) form.
  - IF NO, and another collection cannot be completed within the 48-hour window, reschedule another V3M within the visit window.
  - IF NO, and another collection cannot be scheduled within the 48-hour period and another V3M cannot be completed within the visit window, stop and complete the ASSESS-AKI Withdrawal (WITHDR) form. The participant is ineligible to participate in the study and NO (blood or urine) samples should be entered into the BST.
- Q1040 - 1050. A response should be recorded for each Serum specimen.
- Q1060. Record collection of 3mL specimen for the local lab.
- Q1070 – 1080. A response should be recorded for each EDTA Plasma and DNA specimen.
- Q1090. Record collection of 4.5mL Citrate specimen.
- If one 10mL EDTA purple top vacutainer was not collected, prepare to attempt the DNA collection at V12M.
- Complete the site specific worksheet.
- If another collection is successfully completed within 48 hours of the initial collection, complete the V3M Specimen 2+ Collection:Blood (P1_V3M_COLLECT_BLD_2) form.
  - The 2+ forms should only be entered into the database when the last collection attempt is completed within the 48-hour period.
  - The 2+ forms are entered into the database as single forms.
- If another collection is completed within the V3M visit window, the forms completed at the rescheduled visit will be used for entry into the database and should be sent to the DCC.
  - The original V3M forms can be stored at the site.

2.E.2 P1_V3M_COLLECT_UA

- Complete the Visit Date as the current date the Adult Outpatient V3M Specimen Collection: Urine (P1_V3M_COLLECT_UA) form is completed.
- Q1000. This question is completed for home visits only to indicate if extra time will be allowed between collection and processing.
- Q1020. Record the date of the urine collection. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1030. Record the time urine specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1035. Record the amount of urine collected.
- NOTE: If a participant collects a urine sample at home and brings it to the visit, enter the date sample collected by the participant in Q1020, the time sample collected by the participant in Q1030, and the amount of urine collected by the participant in Q1035. Q1040 will be left missing since PI will not be added to these samples.
- Q1040. Record the time the protease inhibitor was added to the urine specimen samples using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1050. Was the minimum amount of urine (20mL) collected?
  - IF NO, reschedule another collection within 48 hours of this collection and complete the V3M Specimen 2+ Collection:Urine (P1_V3M_COLLECT_UA_2) form.
  - IF NO, and another collection cannot be completed within the 48-hour period, reschedule another V3M within the visit window.
  - IF NO, and another collection cannot be scheduled within the 48-hour period and another V3M cannot be completed within the visit window, stop and complete the ASSESS-AKI Withdrawal (WITHDR) form.
- Complete the site specific worksheet.
- If another collection is successfully completed within 48 hours of the initial collection, complete the V3M Specimen 2+ Collection:Urine (P1_V3M_COLLECT_UA_2) form.
  - The 2+ forms should only be entered into the database when the last collection attempt is completed within the 48-hour period.
  - The 2+ forms are entered into the database as single forms.
- If another collection is completed within the V3M visit window, the forms completed at the rescheduled visit will be used for entry into the database and should be sent to the DCC.
  - The original V3M forms can be stored at the site.

2.E.3 P1_V3M_PROCESS

- Complete the Visit Date as the current date the Adult Outpatient V3M Specimen Processing (P1_V3M_PROCESS) form is completed.
- Q995. Record and enter the urine collection date into the database. This is an additional field included on the Adult Outpatient V3M Specimen 2+ Processing (P1_V3M_PROCESS_2) form.

2.E.3.a Blood Specimen Processing

- Q1000. If there are no blood samples to be processed, complete the site specific worksheet and proceed to Question 1090.
- Q1010. Record the number of aliquots of serum produced from the 9mL SST or 7.5mL double SST red top tubes. The ASSESS-AKI goal is 5 (1.0mL aliquots).
- Q1020. If more than 5 aliquots were produced, estimate the additional amount of serum saved and report to the nearest mL. If Q1010 = 5 AND no additional serum was saved, record 0 in Q1020.
- Q1030. Record the number of 1.0mL aliquots of plasma produced from the 10mL EDTA purple top tubes. The ASSESS-AKI goal is 5 (1.0mL aliquots).
- Q1040. If more than 5 aliquots were produced, estimate the additional amount of plasma saved and report to the nearest mL. If Q1030 = 5 AND no additional plasma was saved, record 0 in Q1040.
- Q1045. Record how many packed cell pellets were produced from the 10mL purple top vacutainer. (1 per tube, ASSESS-AKI goal is 2).
  - If the DNA is not collected at V3M, answer '0' to this question. No rows are entered into the Biological Sample Tracking module. If DNA is not collected at V3M, prepare to attempt the DNA collections at V12M.
  - At V12M, DNA collection should be attempted again.
    - If no DNA is collected, the DNA sample should be entered into the Biological Sample Tracking module at V3M as not collected.
    - If the DNA sample is collected, submit a data correction for the P1_V3M_PROCESS form Q1045 to be updated and enter the DNA sample(s) into the Biological Sample Tracking module at V3M.
    - If a participant withdraws before V12M, the DNA sample will be entered into the Biological Sample Tracking module as not collected at V3M.
  - If DNA_CONSENT Q1000 – Q1030 = 0, DNA samples are not entered into the Biological Sample Tracking module at all.
  - If DNA_DBGAP_CONSENT Q1000 – Q1040 = 0, DNA samples are not entered into the Biological Sample Tracking module at all.
  - For KAISER participants: If DNA_DBGAP_CONSENT Q995 = 1 AND Q1040 = 0 OR if Q995 – Q1040 = 0, DNA samples are not entered into the Biological Sample Tracking module at all.

- Q1050. Record the number of 1.0mL aliquots of plasma produced from the 4.5mL citrate blue top tube. The ASSESS-AKI goal is 2 (1.0mL aliquots).
- Q1060. If more than 2 aliquots were produced, estimate the additional amount of plasma saved and report to the nearest mL. If Q1050 = 2 AND no additional plasma was saved, record 0 in Q1060.
- Q1070. Record the date the aliquots were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1080. Record the time aliquots were frozen using a 24-hour clock. Aliquots should be stored in a -80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.

2.E.3.b Urine Specimen Processing

- Q1090. If there are no urine samples to be processed, complete the site specific worksheet and proceed to the Biological Sample Tracking module and enter all records.
- Q1100. Record the number of 1.0mL aliquots of urine produced. The ASSESS-AKI goal is 10 (1.0mL aliquots).
- Q1110. Record the number of 10mL aliquots of urine produced. The ASSESS-AKI goal is 3 (10mL aliquots).
- Q1120. Record the number of 10mL aliquots of urine with protease inhibitors produced. The ASSESS-AKI goal is 1 (10mL aliquot).
- Q1130. Record the date the aliquots were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1140. Record the time aliquots were frozen using a 24-hour clock. Aliquots should be stored in a -80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- If you need to process/spin the blood or urine samples a second time, include a comment in Q6000.
- If multiple collection attempts are made, complete the V3M Specimen Processing 2+ (P1_V3M_PROCESS_2) form(s).
- When the LAST collection attempt has been completed for the visit, enter all appropriate samples into the Biological Sample Tracking module.

2.E.4 P1_V3M_BLOOD_LOG

- At Visit 3M, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- If multiple collection attempts are completed within the 48-hour period or within the outpatient visit window, multiple logs should be used.

  - Complete one log for each collection date.
  - Use the logs when entering the blood samples into the BST.
- The log(s) will be stored at the clinical center and should not be sent to the DCC.
- The log(s) will be reviewed during ASSESS-AKI site visits.

2.E.5 P1_V3M_URINE_LOG

- At Visit 3M, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- If multiple collection attempts are completed within the 48-hour period or within the outpatient visit window, multiple logs should be used.
  - Complete one log for each collection date.
  - Use the logs when entering the urine samples into the BST.
- The log(s) will be stored at the clinical center and should not be sent to the DCC.
- The log(s) will be reviewed during ASSESS-AKI site visits.

2.F Yearly Visit Forms: ADULTS

2.F.1 P1_OUTPT_COLLECT_BLD

- Complete the Visit Date as the current date the Adult Outpatient Yearly Specimen Collection: Blood (P1_OUTPT_COLLECT_BLD) form is completed.
- Q1000. This question is completed for home visits only to indicate if extra time will be allowed between collection and processing.
- Q1010. Record the date of the blood draw. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1020. Record the time blood specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1030 - 1040. A response should be recorded for each Serum specimen.
- Q1050. Record collection of 3mL specimen for the local lab.
- Q1060 – 1070. A response should be recorded for each EDTA Plasma specimen.
- Q1080. Record collection of 4.5mL Citrate specimen.
- Please note: If DNA collection was not completed at V3M, attempt the collection at V12M. Please refer to section 2.E.3.a. of the Biospecimen MOP for detailed instructions on processing and entry of the DNA specimens.
- Q1030 – Q1080. Were the samples successfully collected?
    - IF NO, reschedule another collection within 48 hours of this collection and complete the Adult Outpatient Specimen 2+ Collection: Blood (P1_OUTPT_COLLECT_BLD_2) form.
    - IF NO, and another collection cannot be completed within the 48-huor window, reschedule another V3M within the visit window.
- Complete the site specific worksheet.
- If another collection is successfully completed within 48 hours of the initial collection, complete the Adult Outpatient Specimen 2+ Collection:Blood (P1_OUTPT_COLLECT_BLD_2) form.
    - The 2+ forms should only be entered into the database when the last collection attempt is completed within the 48-hour period.
    - The 2+ forms are entered into the database as single forms.
- If another collection is completed within the V3M visit window, the forms completed at the rescheduled visit will be used for entry into the database and should be sent to the DCC.
    - The original outpatient visit forms can be stored at the site.

2.F.2 P1_OUTPT_COLLECT_UA

- Complete the Visit Date as the current date the Adult Outpatient Yearly Specimen Collection: Urine (P1_OUTPT_COLLECT_UA) form is completed.
- Q1000. This question is completed for home visits only to indicate if extra time will be allowed between collection and processing.
- Q1020. Record the date of the urine collection. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1030. Record the time urine specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- NOTE: If a participant collects a urine sample at home and brings it to the visit, enter the date sample collected by the participant in Q1020, and the time sample collected by the participant in Q1030.
- Q1040. Were the samples successfully collected?
  - IF NO, reschedule another collection within 48 hours of this collection and complete the Adult Outpatient Specimen 2+ Collection:Urine (P1_OUTPT_COLLECT_UA_2) form.
  - IF NO, and another collection cannot be completed within the 48-huor window, reschedule another V3M within the visit window.
- Complete the site specific worksheet.
- If another collection is successfully completed within 48 hours of the initial collection, complete the Adult Outpatient Specimen 2+ Collection:Urine (P1_OUTPT_COLLECT_UA_2) form.
  - The 2+ forms should only be entered into the database when the last collection attempt is completed within the 48-hour period.
  - The 2+ forms are entered into the database as single forms.
- If another collection is completed within the V3M visit window, the forms completed at the rescheduled visit will be used for entry into the database and should be sent to the DCC.
  - The original outpatient visit forms can be stored at the site.

2.F.3 P1_OUTPT_PROCESS

- Complete the Visit Date as the current date the Adult Outpatient Yearly Specimen Processing (P1_OUTPT_PROCESS) form is completed.
- Q995. Record and enter the sample collection date into the database. This is an additional field included on the Adult Outpatient Yearly Specimen 2+ Processing (P1_OUTPT_PROCESS_2) form.

2.F.3.a Blood Specimen Processing

- Q1000. If there are no blood samples to be processed, complete the site specific worksheet and proceed to Question 1090.

- Q1010. Record the number of 1.0mL aliquots of serum produced from the 9mL SST or 7.5mL double SST red top tubes. The ASSESS-AKI goal is 6 (1.0mL aliquots).
- Q1020. If more than 6 aliquots were produced, estimate the additional amount of serum saved and report to the nearest mL. If Q1010 = 6 AND no additional serum was saved, record 0 in Q1020.
- Q1030. Record the number of 1.0mL aliquots of plasma produced from the 10mL EDTA purple top tubes. The ASSESS-AKI goal is 5 (1.0mL aliquots).
- Q1040. If more than 5 aliquots were produced, estimate the additional amount of plasma saved and report to the nearest mL. If Q1030 = 5 AND no additional plasma was saved, record 0 in Q1040.
- Q1050. Record the number of 1.0mL aliquots of plasma produced from the 4.5mL citrate blue top tube. The ASSESS-AKI goal is 2 (1.0mL aliquots).
- Q1060. If more than 2 aliquots were produced, estimate the additional amount of plasma saved and report to the nearest mL. If Q1050 = 2 AND no additional plasma was saved, record 0 in Q1060.
- Q1070. Record the date the aliquots were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1080. Record the time aliquots were frozen using a 24-hour clock. Aliquots should be stored in a -80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.

2.F.3.b Urine Specimen Processing

- Q1090. If there are no urine samples to be processed, complete the site specific worksheet and proceed to the Biological Sample Tracking module and enter all records.
- Q1100. Record the number of 1.0mL aliquots of urine produced. The ASSESS-AKI goal is 10 (1.0mL aliquots).
- Q1110. Record the number of 10mL aliquots of urine produced. The ASSESS-AKI goal is 4 (10mL aliquots) at V12M, V24M, and V36M.
- Q1120. Record the date the aliquots were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1130. Record the time aliquots were frozen using a 24-hour clock. Aliquots should be stored in a -80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- If you need to process/spin the blood or urine samples a second time, include a comment in Q6000.
- If multiple collection attempts are made, complete the Adult Outpatient Yearly Specimen Processing 2+ (P1_OUTPT_PROCESS_2) form(s).
- When the LAST collection attempt has been completed for the visit, enter all appropriate samples into the Biological Sample Tracking module.

2.F.4 P1_VXXM_BLOOD_LOG

- At yearly outpatient visits, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- If multiple collection attempts are completed within the 48-hour period or within the outpatient visit window, multiple logs should be used.
  - Complete one log for each collection date.
  - Use the logs when entering the urine samples into the BST.
- The log(s) will be stored at the clinical center and should not be sent to the DCC.
- The log(s) will be reviewed during ASSESS-AKI site visits

2.F.5 P1_VXXM_URINE_LOG

- At yearly outpatient visits, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- If multiple collection attempts are completed within the 48-hour period or within the outpatient visit window, multiple logs should be used.
  - Complete one log for each collection date.
  - Use the logs when entering the urine samples into the BST.
- This log will be stored at the clinical center and should not be sent to the DCC.
- This log will be reviewed during ASSESS-AKI site visits.

2.G Storage

The following samples should NOT be frozen from the adult visits:

- 3mL EDTA tube: Should be sent to the local laboratory for CBC

Before April 19, 2010, 2 x 10mL EDTA tubes for DNA from adult participants were shipped to the Central Lab for DNA extraction.

For all other tubes:

- Immediately freeze all other tubes at –80°C after they have been scanned into the ASSESS-AKI Biological Sample Tracking system (BST).
- Store in the upright position until shipped.
- In exceptional cases, when the -80°C freezer is not available or broken, the samples can be stored at -20 for short-term (less than 7 days). Add comment to this effect on Adult Outpatient V3M Specimen Processing (P1 _V3M_PROCESS) or Adult Outpatient Yearly Specimen Processing (P1 _OUPT _PROCESS) forms. Do NOT use a frost-free freezer.

2.H Instructions for Scanning the Biosamples into the Biological Sample Tracking (BST) Module

1. Log into the ASSESS website and select the Application link.
2. Select Launch ASSESS-AKI Application.
3. Log onto the Biological Sample Tracking module.
4. Select the Enter/Update/Search Sample Tracking.
5. Enter your Participant ID and the Visit Number and select the Sample Type.
6. Enter the Collection Date and select 'Execute Query/Insert Samples'.
    - If multiple collection attempts were completed within the 48-hour period or within the visit window, there will be multiple blood/urine specimen logs.
    - If you have multiple collection logs, do not pre-populate the date for all records.
    - Scan each barcode from the logs, adding the collection date(s) as necessary.
7. When your barcodes have been scanned review all of the data on the screen and verify that all the fields are correct.
    - If the default value does not match the volume in the scanned tube, the Sample Volume MUST be changed.
    - Refer to the ASSESS General MOP, Section 10.B.5 for detailed instructions on updating the samples.
8. When the information matches the log and is correct for all fields, select Insert Samples.
9. Next Exit out of the 'Enter/Update/Search' Sample Tracking and go to the 'Build a Shipment' Link.
10. Scan or enter your barcode IDs from the P1 _V3M_BLOOD_LOG(S)/ P1_VXXM_BLOOD_LOG and P1 _V3M_URINE_LOG(S)/P1_VXXM_URINE_LOG for the biosamples, again you should see these records appear below with the information.
11. Once the records appear on the screen, select the 'Exit Build Shipment' link.
12. Next go into the View Shipments – Mark as Shipped/Print Logs.
13. You should see your build in progress, select the Ship button.
14. Enter a Date Shipment Sent, the tracking number, comments and select Save.
15. Select the Print Log link and save the file to your desktop and/or print and scan a copy. Also select the Create Export File link. Save this file to your desktop.
16. Email the appropriate lab and copy the ASSESS_LAB alias once your shipment is ready and will be sent out that day with the appropriate lab shipping (instructions found below in Section 5).

3 BIOSPECIMENS: INPATIENT PEDIATRIC VISITS

3.A Overview

Figure 3.1 and 3.2 demonstrate the biospecimen collection related to the hospital, or inpatient, visit. Detailed procedures for collection, urine analysis, processing, storage, and shipping are described in this section.

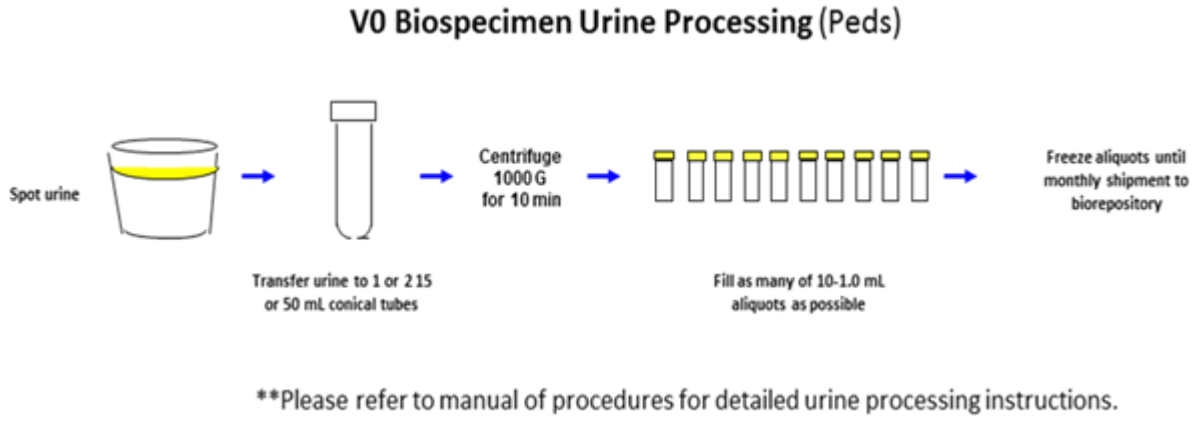
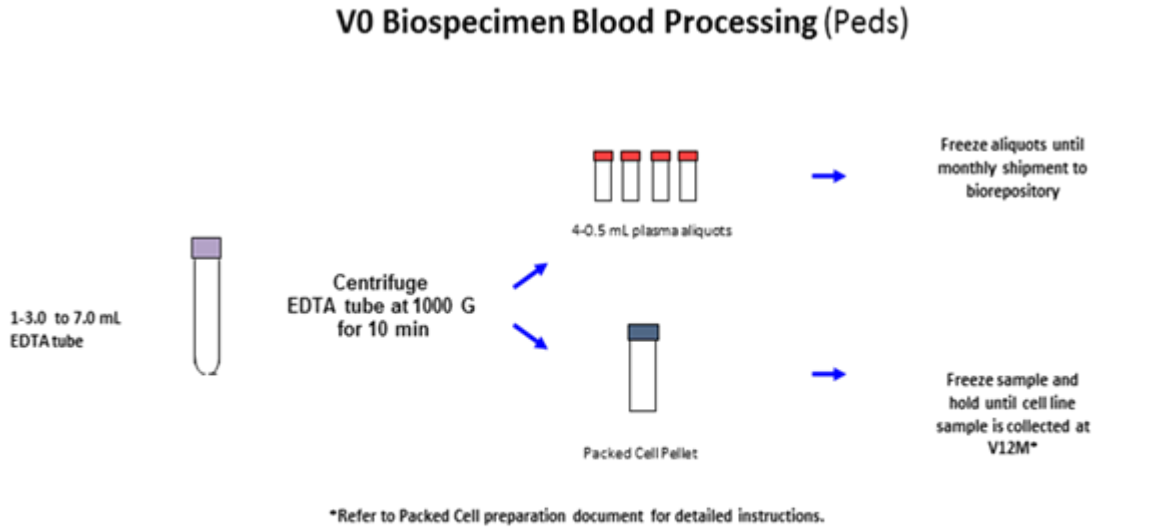


Figure 3.1. Biospecimen Blood Processing (Peds)



* Sample will be used as a backup DNA source if cell line sample can not be obtained at V12M.
**Please refer to manual of procedures for detailed blood processing instructions.

Figure 3.2. Biospecimen Urine Processing (Peds)

It is best to collect blood and urine on the same day. In rare circumstances, it should be ok to process different days of urine (Day 2) and blood (Day 3); if the participant is an AKI participant, both samples must be collected within the 96-hour window after the AKI event. This is for uncommon circumstances due to blood collection issues and oliguria in the first 48 hours.

3.B Blood Collection

- The inpatient blood draw will be collected in a single lavender top tube supplied by the ASSESS-AKI recruiter. Depending on the study site, this blood draw may be collected by an intensive care unit nurse, study coordinator, or the hospital phlebotomy department. There is no minimum plasma volume for pediatric participants. However, if the child weighs less than 15 kg, an attempt to collect 1 to 3mL should be made (not to exceed 3mL); if the child weighs more than 15 kg, an attempt to collect 5mL of blood should be made.
- In all cases, samples should be spun, aliquoted, and frozen as quickly as possible (see 3.D Processing), within six hours. If samples will not be processed within 30 minutes, place on ice immediately until the samples are spun, aliquoted, and frozen. For the Inpatient Phase, all aliquots will be sent to the NIDDK Biorepository only; there is no prioritization scheme.

3.B.1 Label Preparation: Vacutainers

- Print the vacutainers labels for each participant to facilitate accurate tracking of collected specimens.
- Pre-label the vacutainers.

3.C Urine Collection

- In all cases, the freshest urine should be collected. The suggested minimum volume for collection is 2mL for pediatrics.
- In all cases, samples should be spun and frozen as quickly as possible (see 3.D Processing), within six hours. If samples will not be processed within 30 minutes, place on ice immediately until the samples are spun, aliquoted, and frozen.

3.C.1 Indwelling Urine Catheter

If the participant has an indwelling urinary catheter, urine should be collected from the urine meter or the port on the catheter tubing, not from the large drain bag, within a two-hour window. We recommend clamping the Foley tubing and then using a needleless system to get urine from the tube side port. A nurse caring for the patient or a trained study coordinator may collect this specimen.

1. Place a clamp (e.g., a blue plastic clamp) on the tubing to block the flow of urine into the bag.
2. Wipe the needleless port on the Foley catheter bag with an alcohol wipe and allow it to dry.
3. Access the needleless port with a Luer-lock tip syringe and aspirate back urine.
4. Transfer contents to urine container for transport back to the processing lab.

3.C.2 Clean Catch Void

If the participant is spontaneously voiding, ask him/her to do a clean catch void. Do not take urine from participants who have urostomy bags. Procedures for collecting a clean catch void are outlined below.

3.C.2.a Urine Collection Items:

- Three special towelettes for midstream urine collection.
- 5 oz wide mouthed cup for specimen collection.

3.C.2.b Clean Catch Instructions for Males:

1. Make sure the bladder is somewhat full.
2. Wash hands thoroughly with soap and water.
3. Retract the foreskin completely, if present.
4. Clean the end of the penis with special towelettes beginning at the urethral opening. Wipe in a circular motion AWAY from the opening.
5. Repeat the above procedure using two successive towelettes.
6. Void into toilet for a few seconds and then stop. Do NOT collect the first amount of urine. Restart urine stream and collect about ½ cup in the sterile container provided.
7. Void the remainder of urine into the toilet.

8. Cap and avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
9. Bring the container to the study personnel.

3.C.2.c Clean Catch Instructions for Females:

"Clean catch" means that the urine sample is not contaminated with any vaginal discharge, menstrual blood, or bacteria.

1. If there is vaginal discharge or the participant has her period, insert a fresh tampon into the vagina.
2. Wash hands thoroughly with soap and water.
3. Spread labia with 1 hand and hold apart for collection.
4. Use three special towelettes to clean area.
5. Wipe down one side, front to back, with one towelette.
6. Wipe down other side, front to back, with second towelette.
7. Wipe down center, front to back, with last towelette.
8. Void into toilet for a few seconds and then stop. Do NOT collect the first amount of urine. Restart urine stream and collect about ½ cup in the sterile container provided.
9. Void the remainder of urine into the toilet.
10. Cap and avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
11. Bring the container to the study personnel.

3.C.3 Participants Unable to Perform a Clean Catch Void

If the participant is spontaneously voiding but unable to perform a clean catch void due to physical constraints (weakness, deconditioning), collect urine as follows.

1. Do not have the participant use cleaning towelettes, as the cleaning agents in the towelettes may interfere with some sensitive bioassays.
2. Have the participant void into a urinal (men) or a clean hat on the toilet or on a commode (men or women).
3. Do not collect urine from a hat that is contaminated with stool.
4. Study personnel should pour a small amount of urine into a labeled specimen cup.
5. Cap the container; avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
6. Record that the urine was not a clean catch specimen in the comment section of the Pediatric Inpatient Specimen Collection Form (P2_INPT_SPEC).

3.C.4 Cotton Balls Urine Collection if there is no Urine Catheter

If the participant is wearing a diaper, the urine can be collected by inserting cotton balls in the diaper. Procedures for collecting urine from cotton balls are outlined below:

3.C.4.a Urine Collection Items:

- Jumbo size cotton balls.
- Plastic cling wrap of standard width (e.g. Saran Wrap).
- 5 oz wide mouthed cup for specimen collection.

3.C.4.b Instructions for Cotton Ball Urine Collection:

1. Prepare the collection cup containing the cotton balls:
2. Cut-out a piece of plastic wrap (approximately 7 inches in length).
3. Place 3 to 4 jumbo sized cotton balls in the center of the plastic wrap (number of cotton balls to be used is dependent on the size of the patient: for infants use three (3) cotton balls and for young children use four (4) cotton balls). Gently enclose the corners of the plastic wrap over the cotton balls.
4. Place the plastic wrapped cotton balls in the specimen collection container.
5. Bring the collection cup to the bedside nurse or legal guardian and explain the procedure of inserting the cotton balls into the diaper (see Figure 3.3 below for a schematic view of the procedure).
6. Remove the plastic-wrapped cotton balls from collection cup.
7. In a new diaper, unwrap the cotton balls by ensuring to keep the cotton balls centered and on top of the plastic wrap.
8. Put diaper on patient as usual, and ensure the alignment of the cotton balls to the area of urine collection in the diaper (i.e. centered for female patients and towards the front of the diaper for male patients).
9. Ask the legal guardian or nurse to check the diaper regularly to avoid fecal contamination of the cotton balls.
10. To remove the cotton balls, simply re-wrap the cotton balls in the plastic wrap and place in the collection cup.
11. To extract urine from the cotton ball, simply squeeze the cotton balls into the collection cup, either manually (always wear gloves) or by using a needleless syringe.

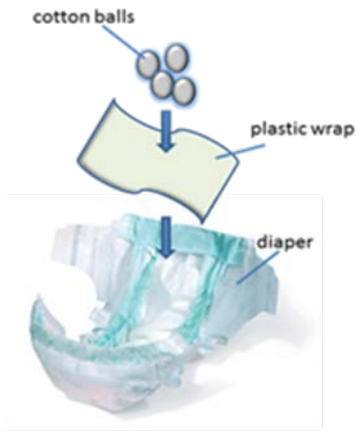


Figure 3.3. Diagram illustrating the insertion of cotton balls in a diaper for urine collection.

*3.D **Processing***

The processing of specimens will be within six hours of collection. Blood and urine biospecimens should be stored on ice or refrigerated until processed. Follow the instructions below to centrifuge and aliquot the blood and urine specimens for the inpatient visit.

3.D.1 Gather Equipment and Supplies

- Centrifuge
- Transfer pipettes
- Aliquot rack
- 14-16 2mL cryogenic vials
- 15mL or 50mL conical tubes for centrifugation.
- Balance tubes for centrifugation.
- Waste disposal containers and sharps container
- Cardboard freezer and transport boxes
- Freezer at -80ºC
- Safety: Obtain and utilize necessary protective clothing/equipment for preparing an aliquot of specimens. Such items include but are not limited to lab coats, gloves, protective eyewear, and absorbent pads.

3.D.2 Safety Precautions for Handling Blood and Urine Specimens

- All specimens are handled as potentially infectious for laboratory workers. Transmissions of the infectious agents associated with Hepatitis and HIV via “needle stick” skin punctures have been documented.
- Where feasible, wear disposable plastic gloves when collecting and processing specimens. Alternatively, wash hands thoroughly with disinfectant soap prior to leaving the work area. Skin cuts or abrasions should be covered.
- Aliquot/process specimens within a biological safety cabinet.
- Use 0.1% sodium hypochlorite (household bleach) to clean up any spills of blood, plasma, or serum. Use this solution to clean up all laboratory work surfaces at the completion of work activities.
- Dispose of all needles and tubing in puncture-resistant sharps containers for safe disposal.
- Do not perform any pipetting by mouth.
- Avoid formation of potentially infectious aerosols by careful pipetting and centrifugation.
- All used vacutainers tubes, needles, and blood products are to be placed in spill proof liquid biohazard sharps containers for disposal.

3.D.3 Centrifuge Instructions

1. Separate and sort any specimens that are not centrifuged (i.e. DNA samples or samples to be sent directly to the local lab).
2. Balancing the centrifuge ensures proper performance of the instrument. Determine the amount of sample volume in each tube and find another tube filled to approximately the same level to ensure correct balancing.
3. Use a "balance tube" filled with water to the proper level if there are an uneven number of specimens.
4. After pairing the tubes by their sample volume, place them into the centrifuge using the following guidelines:
    - If the centrifuge contains buckets, position the tubes in the buckets so that the tube and its match are located in opposite buckets (mirror image of each other). Select holes in the opposing buckets that allow for equal weight distribution. See Figure 3.4.
    - Once the centrifuge is loaded with samples, set the speed for 1000 g, room temperature, and time for 10 minutes. Start the centrifuge.
    - Once the centrifuge is stopped, open the centrifuge and remove the specimens.
    - Locate and arrange the specimens by participant to keep each set of specimens and aliquots organized.
    - Aliquot and freeze all biospecimens.
    - If a urine specimen did not pellet properly, go ahead and aliquot and freeze the biospecimen. Do not re-centrifuge. Add this to the comments section (6000) of the Pediatric Inpatient Specimen Collection Form (P2_INPT_SPEC).
    - If a blood specimen did not pellet properly, re-spin at 2000 g for 15 minutes, ideally in a refrigerated centrifuge. Add this to the comments section (6000) of the Inpatient Specimen Collection Form (P2_INPT_SPEC).

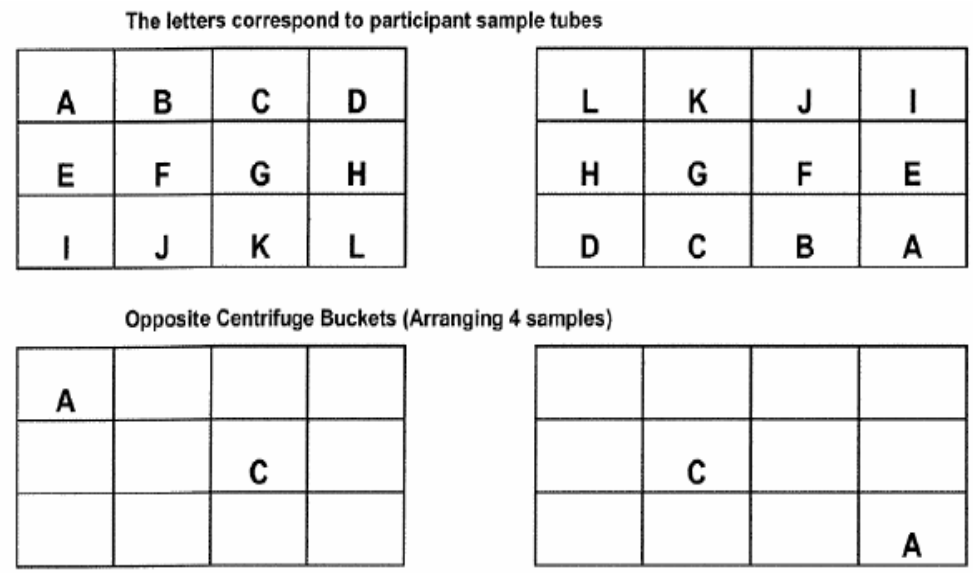


Figure 3.4. Centrifuge Bucket

3.D.4 Create Barcode Labels

The barcode labels will be printed by the individual sites. If additional barcode labels are necessary, allow a three, work-day window for the DCC to obtain and ship labels to the sites.

1. The sites will access the Barcodes link on the main website under Direct Module Access.
2. In the Barcode Label Generator screen, the protocol number and center number will populate with the correct information.
3. Select a Print Type of New if this is a new sheet of labels or Re-Print if you are reprinting a label sheet that has already been generated.
4. If Print Type is Re-Print, then the First Urine Sequence needs to be entered to match the first urine sequence on the label sheet (i.e., if AKU0005061 is first urine sequence, then enter 0005061 into the First Urine Sequence field). The first plasma sequence needs to match the first sequence for the EDTA plasma at Visit 0 and will follow the logic that the first urine sequence did. Note: It is imperative that you know the first urine AND first plasma sequence in order to reprint labels, if there is any question about those numbers, simply create a new label sheet and over label the samples, rather than possibly duplicate a barcode number.
5. Once the information is entered, select Generate Labels.
6. A .cfm page will appear in Adobe .pdf format where the labels will populate one sheet of labels for one participant at Visit 0.
    - Adobe upgrades can affect the label printing.
    - Sites have reported labels printing offline and therefore labels are wasted.

- Whenever you have upgrades at your site, please print the labels on a blank piece of paper to make sure that alignment is still good.
- If you find that the alignment is off, you can adjust the settings on the print preview screen and print again.
- The most common default on the print preview screen is 'actual size' however this may no longer work when upgrades are distributed for Adobe. Try 'fit' and 'shrink oversized pages'. Either of these settings should allow the labels to align and print correctly on the label sheet.

7. Place the blank label sheet in the laserjet printer face down and print the labels.
8. One label sheet will be printed for each adult participant along with a P2_INPT_SPEC_LOG.

3.D.5 Prepare an Aliquot Sample

- Aliquot samples are necessary any time the original specimen collection tube or container cannot be used for storing the specimen.
- Verify that the specimens have been properly centrifuged and cells have been clearly separated.
- Use a disposable transfer pipette to transfer the sample from the primary tube to the appropriately labeled secondary tubes, in this case 2 mL cryogenic vials.
- When removing plasma or serum using a transfer pipette, be very careful not to disturb the buffy coat (white cell layer) or the serum separator layer.
- Store all aliquots in a plastic rack or cardboard freezer box in an upright position at -80°C immediately. Label the racks or cardboard boxes with permanent marker or an adhesive label that say "ASSESS-AKI Inpatient Biospecimens.

3.D.6 Aliquot Instructions for the Inpatient Visit

Before aliquotting, affix all barcoded labels lengthwise on the tube for ease of scanning at the sites and the NIDDK Biorepository/central lab/other partner laboratories. It is required to affix the clear adhesive label over the barcode label while overlapping the ends of the clear adhesive label. Make sure that the label does not overlap on top of the barcode because that may interfere with scanning the barcode.

3.D.6.a General Instructions

- Using a pipette, transfer the supernatants to the 2 mL aliquot tubes provided.
- Be careful not to disrupt any cellular debris at the bottom of the tube.

3.D.6.b Blood Instructions

1. Place tubes into the centrifuge and spin for ten minutes at 1000 g in a room temperature centrifuge.
2. Pipet 0.5mL of plasma into each barcode-labeled 2mL cryovial.

3. Fill as many of the four (4) cryovials as possible. Vials should be filled with exactly 0.5mL. (Exception: At the pediatric sites, try as much as possible to fill the last cryovial with 0.5mL, but it is OK to under fill.)
4. Any leftover blood after aliquoting is completed may be discarded or stored at site.
5. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST).
6. Put into a labeled box and place them into the freezer for monthly shipment.

3.D.6.c Packed Cell Pellet for DNA Extraction

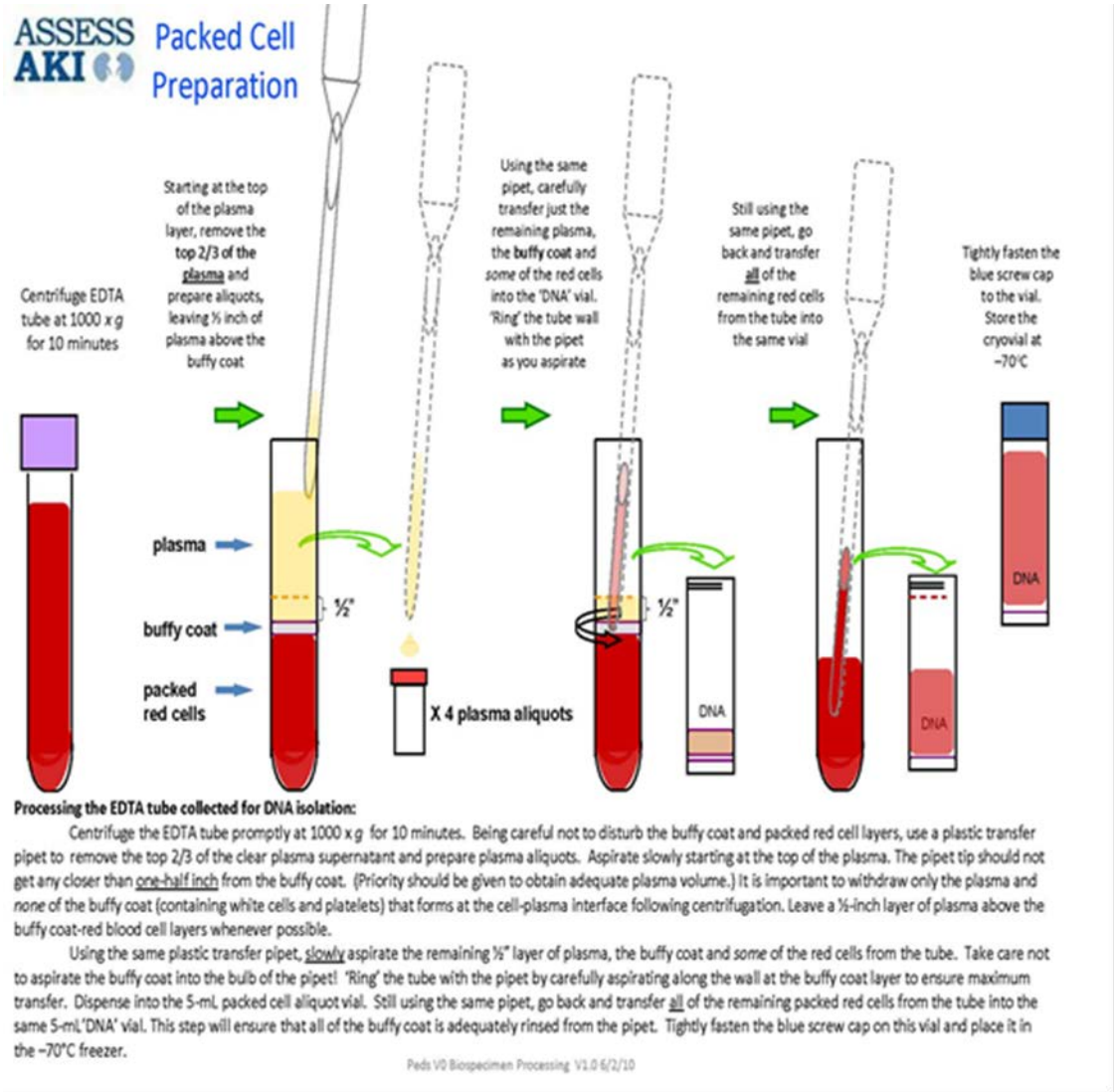


Figure 3.5. Packed Cell Preparation

At the inpatient visit only, transfer the cell pellet to a labeled cryovial for DNA extraction. To collect the cell pellet:

- Using a soft bulb plastic transfer pipette, slowly aspirate the remaining ½" layer of plasma, the buffy coat and *some* of the red cells from the tube. Take care not to aspirate the buffy coat into the bulb of the pipette 'Ring' the tube with the pipette by carefully aspirating along the wall at the buffy coat layer to ensure maximum transfer.
- Dispense into the 5mL packed cell aliquot vial.
- Still using the same pipette, go back and transfer all of the remaining packed red cells from the tube into the same 5-mL'DNA' vial. This step will ensure that the entire buffy coat is adequately rinsed from the pipette.
- Do not transfer just the buffy coat, since there are some white blood cells in the red cell pellet and transferring the entire cell pellet increase the yield.
- Scan samples into ASSESS-AKI Biological Sample Tracking system (BST) if the participant withdraws from ASSESS-AKI prior to V12M, if the cell line collected at V12M/V24M is not adequate for Rutgers lab, or if the participant withdraws between V12M and V24M and the cell line is not collected. A reminder will be given on the V12M visit procedure checklist to verify if the DNA packed cell needs to be entered into the BST module and sent to the Central Lab.
- Put the cryovials into a labeled box and place them into the freezer for weekly shipment to the Central Lab.
- After March 2018, Precision for Medicine replaced Rutgers as the NIDDK Biorepository.

3.D.6.d Urine Instructions

1. Place the spot urine collection in one 50mL conical vial labeled with the participant's ID.
2. Centrifuge for ten (10) minutes at 1000g in a room temperature centrifuge.
3. Pipet 1mL of supernatant into each barcode-labeled 2mL cryovial.
4. Fill as many of the ten (10) cryovials as possible. Vials should be filled with exactly 1.0mL. Do not fill a cryovial with less than 1.0mL.
5. Any leftover urine after aliquoting is completed may be discarded or stored at site.
6. Affix the duplicate barcode label for each sample on the P2_INPT_SPEC_LOG for each participant by sample type and aliquot number.
7. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST) using the P2_INPT_SPEC_LOG.
8. Put into a labeled box and place them into the freezer for monthly shipment.
9. Any remaining urine can be discarded.

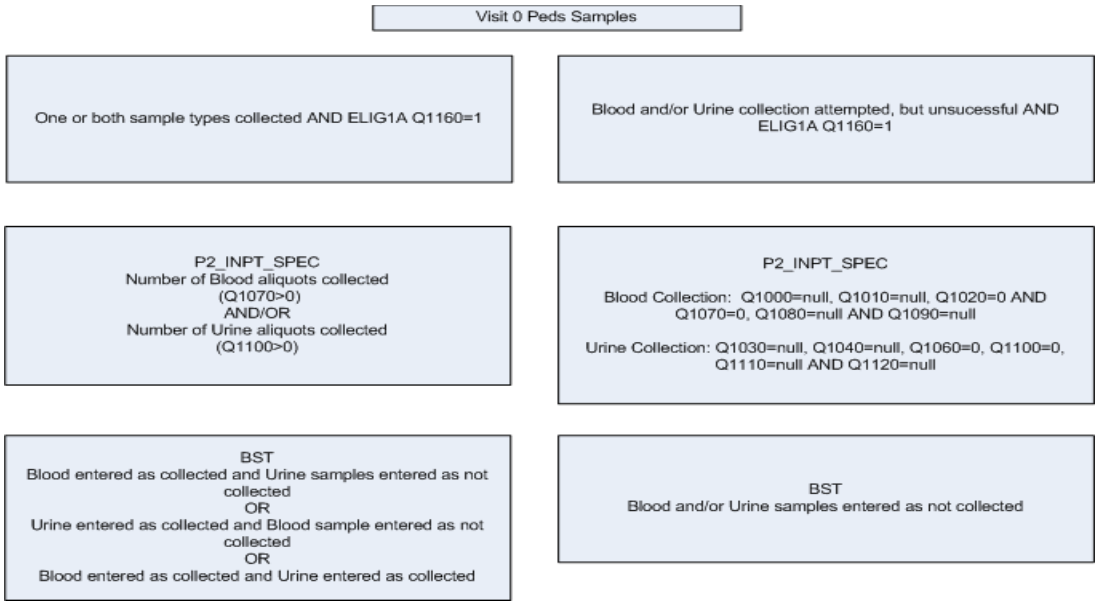
3.E Visit Zero Forms: PEDIATRICS

3.E.1 P2_INPT_SPEC

- Complete the Visit Date as the current date the Pediatric Inpatient Specimen Collection (P2_INPT_SPEC) form is completed.
- Q1000. Record the date of the blood draw. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1010. Record the time blood specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1020. Record the amount of blood collected in milliliters.
- Q1030. Record the date of the urine specimen collection. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1040. Record the time urine specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1050. This question is regarding urine collection from a Foley catheter.
- Q1060. Record the amount of urine collected in milliliters.
- Q1070. Record how many 0.5 ml aliquots of plasma were produced. The ASSESS-AKI goal is 4 (0.5 ml aliquots) for pediatric participants. There is no minimum plasma collection volume for pediatric participants.
- Q1080. Record the time plasma samples were frozen using a 24-hour clock. Aliquots should be stored in a -80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1090. Record the date the plasma samples were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1100. Record how many 1 ml aliquots of urine were produced. The ASSESS-AKI goal is 10 (1 ml aliquots) for all participants, however, there is no minimum collection volume goal.
- Q1110. Record the time urine samples were frozen using a 24-hour clock. Aliquots should be stored in a --80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1120. Record the date the urine samples were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- After the aliquots are produced, enter the aliquot information into the ASSESS-AKI Biological Sample Tracking Module.

3.E.2 Sample Entry Scenarios

- If one sample type is collected and the participant is deemed eligible according to the Eligibility Checklist 1A (ELIG1A Q1160 = 1), complete the P2_INPT_SPEC form and enter samples into the Biological Sample Tracking (BST) module. The samples that were successfully collected are entered as collected, and the unsuccessful sample collection is entered as NOT COLLECTED.
- If a collection was attempted but unsuccessful, and the participant is eligible according to the Eligibility Checklist 1A (ELIG1A Q1160 = 1), complete the P2_INPT_SPEC form and enter samples into the Biological Sample Tracking (BST) module as NOT COLLECTED.
- If both sample types indicate the participant is eligible and the participant is eligible according to the Eligibility Checklist 1A (ELIG1A Q1160 = 1), complete P2_INPT_SPEC form and enter samples into the Biological Sample Tracking (BST) module.
- If ELIG1A indicated ineligibility (Q1160 = 0) AND no samples were collected, the P2_INPT_SPEC form will not be completed and no data will be entered into the study database or the BST.



* If ELIG1A indicated ineligibility (Q1160=0) AND no samples were collected, no data will be entered into the study database or BST

3.E.3 P2_INPT_DNA_SPEC

- Complete the Visit Date as the current date the Inpatient Specimen Collection (INPT_SPEC) form is completed.
- Q1000. Record the date of the blood draw. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1010. Record if the EDTA (purple-top tube) 3 – 7mL for DNA was collected.

- DO NOT enter the DNA sample into the Biological Sample Tracking module until it is determined that the DNA sample at V12M or V24M was not collected.
- If DNA_CONSENT Q1000 – Q1030 = 0, DNA samples are **not** entered into the Biological Sample Tracking module at all.
- Hold the specimen in the site freezer until Rutgers Biorepository Rutgers (Precision for Medicine after March 2018) confirms receipt of ACD-A or Visit 12M/24M collection could not occur. If the participant withdraws from ASSESS-AKI prior to V12M, if the cell line collected at V12M/V24M is not adequate for Rutgers lab Rutgers (Precision for Medicine after March 2018), or if the participant withdraws between V12M and V24M and the cell line is not collected, the DNA packed cell from V0 needs to be entered into the BST module and sent to the Central Lab. Refer to Section 5.C. for Central Lab shipping instructions.

3.E.4 P2_INPT_BLOOD_LOG

- At Visit 0, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- This log will be stored at the clinical center and should not be sent to the DCC.
- This log will be reviewed during ASSESS-AKI site visits.

3.E.5 P2_INPT_LOG

- At Visit 0, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- This log will be stored at the clinical center and should not be sent to the DCC.
- This log will be reviewed during ASSESS-AKI site visits.

3.F Storage

Store all specimens:

- Immediately freeze all tubes at –80°C after they have been scanned into the ASSESS-AKI Biological Sample Tracking system (BST).
- Store in the upright position until shipped.

3.G Instructions for Scanning the Biosamples into the Biological Sample Tracking (BST) Module

1. Log into the ASSESS website and select the Application link.
2. Select Launch ASSESS-AKI Application.
3. Log onto the Biological Sample Tracking module.
4. Select the Enter/Update/Search Sample Tracking.
5. Enter your Participant ID and Visit Number 0 and select the Sample Type.
6. Enter the Collection Date and select 'Execute Query/Insert Samples'.
7. When your barcodes have been scanned review all of the data on the screen and verify that all the fields are correct.
    - If the default value does not match the volume in the scanned tube, the Sample Volume MUST be changed.
    - Refer to the ASSESS General MOP, Section 10.B.5 for detailed instructions on updating the samples.
8. When the information matches the log and is correct for all fields, select Insert Samples.
9. Next Exit out of the 'Enter/Update/Search' Sample Tracking and go to the 'Build a Shipment' Link.
10. Scan or enter your barcode IDs from the P2_INPT_BLOOD_LOG and P2_INPT_URINE_LOG for the biosamples, again you should see these records appear below with the information.
11. Once the records appear on the screen, select the 'Exit Build Shipment' link.
12. Next go into the View Shipments – Mark as Shipped/Print Logs.
13. You should see your build in progress, select the Ship button.
14. Enter a Date Shipment Sent, the tracking number, comments and select Save.
15. Select the Print Log link and save the file to your desktop and/or print and scan a copy. Also select the Create Export File link. Save this file to your desktop.
16. Email the appropriate lab and copy the ASSESS_LAB alias once your shipment is ready and will be sent out that day with the appropriate lab shipping (instructions found below in Section 5).

4 BIOSPECIMENS: OUTPATIENT PEDIATRIC VISITS

4.A Overview

Figures 4.1 and 4.2 below demonstrate the biospecimen collection related to the 3-month (Visit 3M), 12-month (Visit 12M), and subsequent annual outpatient pediatrics visits (Visits 24M, 36M, 48M, 60M, 72M, and 84M.). Detailed procedures for collection, urine analysis, processing, storage, and shipping are described in this section.

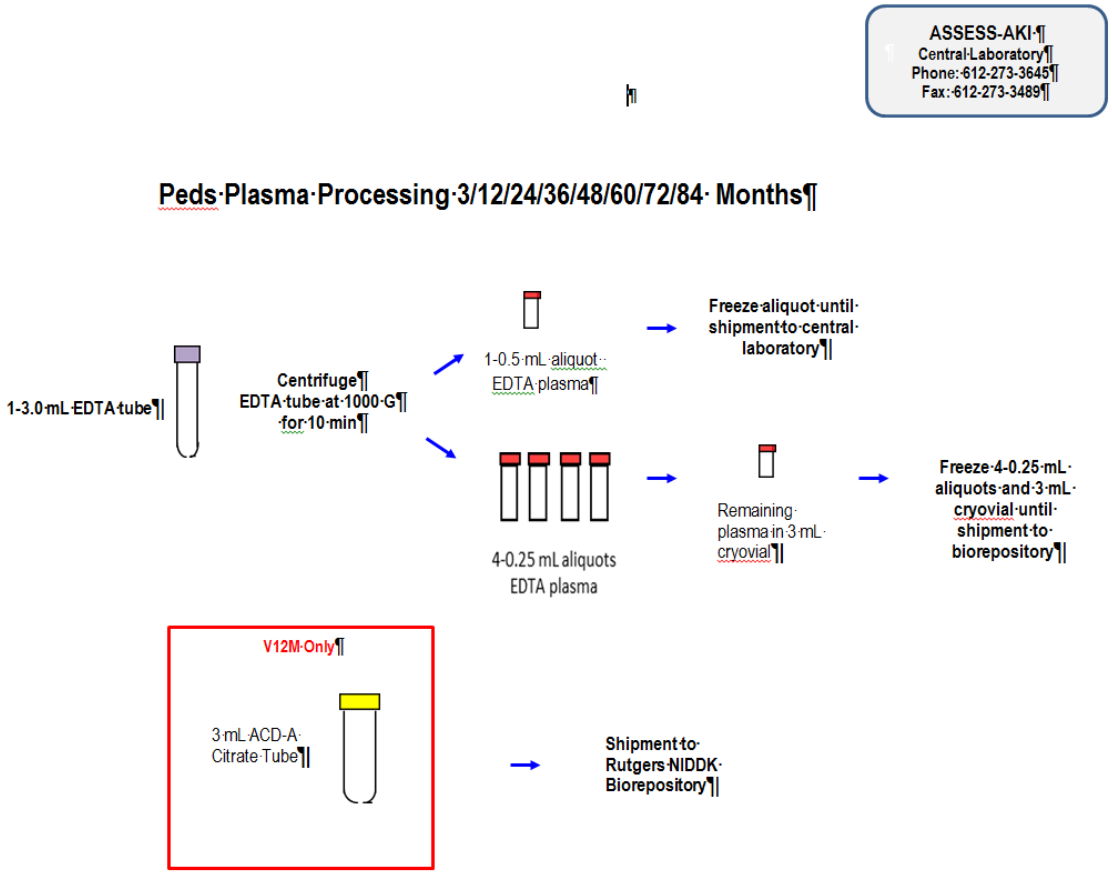


Figure 4.1. Biospecimen collection of Plasma related to the pediatric 3/12/24/36/48/60/72/84-month visits

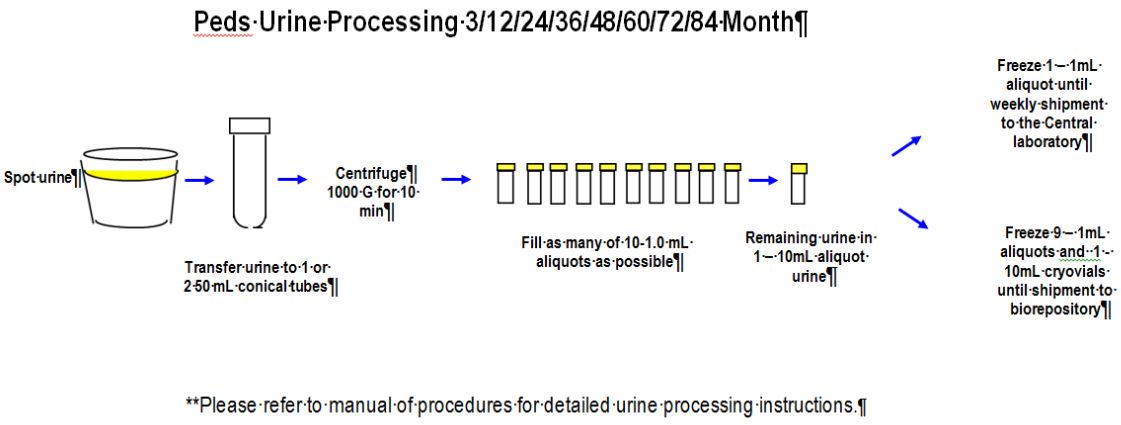


Figure 4.2. Biospecimen collection of Urine related to the pediatric 3/12/24/36/48/60/72/84-month visits.

4.B Blood Collection

- This blood draw will be collected by a research coordinator or other qualified staff at all sites. For pediatric participants, blood will be drawn into a lavender-top EDTA tube, though the size and type of this tube will vary depending on the weight and age of the pediatric participant.
- For all pediatric visits, only EDTA plasma (purple top) tubes will be drawn. The size and type of tube (capillary tube versus vacutainer) will depend on the weight of the pediatric participant. Given the proximity of the V3M outpatient visit to the inpatient visit during which participants are likely to become quite anemic, no more than 3cc of blood will be drawn at V3M from participants less than 15kg, and no more than 5cc of blood will be drawn from participants 15 kg or greater in weight. At V12M, one 3mL ACD-A citrate (yellow top) tube will be collected for cell immortalization by the Rutgers (Precision for Medicine after March 2018) only if consent for DNA collection was obtained by the family.
- The blood samples should be aliquoted per date and time of collection. Refer to the Appendix for Charts E-H, J-M.
- At Visit 12M, there is a mandatory minimum of 0.175mL of plasma based on 0.150mL to measure serum creatinine and serum Cystain C and 0.025mL for core/Tier 1 biomarker measurements. Please attempt to collect a minimum of 0.2mL so that 0.05 may be sent to the NIDDK Biorepository.
- In all cases, samples must be spun, aliquoted, and frozen as quickly as possible (see Processing section), within a target of less than six (6) hours after collection, with the exception of the V12M ACD-A citrate tube that is sent directly and unprocessed to Rutgers (Precision for Medicine after March 2018). If samples will not be processed within 30 minutes after collection, samples should be placed on ice immediately after collection until the samples are spun, aliquoted and frozen at -80ºC. If samples will not be processed within 2.5 hours (from the time that the blood is drawn until processing is started), serum samples are to be processed in the field using battery operated centrifuges, if at all possible and using double serum separator tubes. Plasma and urine tubes will be spun and processed at the Clinical Research Center Laboratory, with the exception of the V12M ACD-A citrate tube that is sent directly and unprocessed to Rutgers (Precision for Medicine after March 2018).

4.B.1 Biosample Prioritization

For the outpatient phase, the top priority is sending a single aliquot of EDTA plasma and a single aliquot of urine from pediatric participants to the Central Laboratory at all visits. All other aliquots will be sent to the NIDDK Biorepository or Rutgers (Precision for Medicine after March 2018) for the V12M ACD-A tube.

- If only the mandatory minimum of 0.175mL of plasma is collected at V12M, 0.150mL aliquot of plasma should be sent to the Central Lab and 0.025mL of plasma sent to the NIDDK Biorepository for core/Tier 1 biomarker measurements. This same scheme should be followed for Visit 3M, Visit 24M, Visit 36M, Visit 48M, Visit 60M, Visit 72M, and Visit 84M if 0.175mL of plasma is collected.
- If more than 0.175mL of plasma is collected, but the goal amount (0.5mL) of plasma was not reached, one 0.150mL aliquot of plasma should be sent to the Central Lab and the remaining plasma sent to the NIDDK Biorepository.

4.B.2 Label Preparation: Vacutainers

- Print the vacutainers labels for each participant to facilitate accurate tracking of collected specimens.
- Pre-label the vacutainers with site-specific labels.

4.B.3 Equipment Preparation

Blood collection tray items for all participants:

- A test tube rack to hold the blood collection tubes which are drawn from each participant; these tubes are described in detail in the next section.
- A plastic vacutainer tube guide
- Three vacutainer Luer slip adaptors to connect the butterfly
- Sterile alcohol swabs
- Gauze sponges
- A tourniquet
- Bandages (Band Aids)
- A stopwatch
- Waste disposal container for sharps

4.B.4 Blood Collection Tray Items for Pediatrics

- Age-specific blood collection materials expected to be required (capillary specimen: finger-poke device and purple-top capillary blood collection tube; only for V12M: 3mL ACD-A citrate (yellow top) vacutainer; venous specimen: 21 gauge or smaller butterfly needle with plastic tubing adaptor and 5cc syringe). If unsure, be ready to perform both types of blood draw.
- If required, local anesthetic cream (EMLA or Ametop).
- If performing a home visit, blood-absorbing blue diaper pad.
- Sample aliquot tray items:
  - A rack to hold the aliquot vials, in the same order as the blood collection tubes are drawn
  - Pipetman and pipet tips
  - Soft bulb transfer pipettes to transfer cell pellet
  - Absorbent pads to minimize splashing when opening blood collection tubes
  - 2 mL and 10 mL aliquot cryovials are provided by the NIDDK Biorepository
  - Red inserts are provided for the clear cap of the blood aliquot cryovials: if the site chooses to use the inserts, the red insert should be applied to all blood aliquot cryovials. Use of the colored inserts is not mandatory.
  - Biohazardous waste disposal container

4.B.5 Blood Collection Preparation

Preparation for specimen collection is done in the following manner in the early morning, prior to arrival of any participants.

1. Check to make sure the blood collection tray is properly equipped. Every item on the checklist must be ready before proceeding.
2. Check that each vacutainer tube is properly labeled with the appropriate participant number.
3. Check that the sample processing tray is properly equipped. Every item on the checklist must be ready and in its proper position.
4. Check that the aliquot processing tray is properly equipped. Every item on the checklist must be ready and in its proper position.
5. Check that each collection tube and aliquot tube is labeled with the appropriate participant identification number.
6. Check that the centrifuge is working properly.
7. Check the freezer temperature (-80ºC).

Phlebotomy Room:

1. The blood draw should take place in an isolated room or participants should be separated by room dividers.
2. The room must be equipped with all of the necessary blood specimen supplies.
3. A separate counter or worktable must be equipped with all of the materials and vials that are used in the blood handling and processing.
4. The centrifuge and freezer should be nearby.

4.B.6 Participant Preparation

- Anticipate at least 15 minutes per participant.
- At participant arrival:
  - Check that each blood collection tube is labeled with the participant's name/medical record number or participant ID.
  - Check that the aliquot tubes are prepared and labeled correctly.
- Participant Preparation:
  - Informed consent must be obtained by the trained staff member before drawing blood. This procedure is followed to ensure that the participants understand the purpose of blood drawing and the possible complications of venipuncture. A standard informed consent has been prepared for this study at each participating site. With regard to laboratory procedures, the consent statement informs study participants that there is a small risk of bruising at the spot on the area where the blood is taken. The consent statement also informs study participants that a

copy of the test results is sent to their physician, and that they will be contacted if clinically important tests are abnormal.

- The participant is asked whether he/she has a bleeding disorder before the blood is drawn. If such a disorder is present, ask the participant whether he/she has had blood drawn previously and if so, whether he/she had any problems with excessive bleeding or bruising at the venipuncture site. If the participant has a history of venipuncture problems, the participant should be sampled only if approved by the physician.
- Ask the participant if they or their doctor have a preference as to which vein to use to determine whether or not they have been told to protect a particular vein or particular upper extremity.
- If not, it is recommended that the medial-most antecubital vein in the dominant arm is used, assuming that the non-dominant arm will be the access arm of choice if the subject goes on to need dialysis, and that the medial most antecubital vein is not likely to be the draining cephalic vein.
- The venipuncture is performed with a 21 gauge (or smaller) butterfly needle with 12 inches of plastic tubing between the venipuncture site and the blood collection tubes. The butterfly has a small, walled needle which minimizes trauma to the skin and vein. The use of 12 inches of tubing allows tubes to be changed without any movement of the needle in the vein. If the participant is concerned about the venipuncture, he/she may be reassured to know such care is taken.
- The participant should be given enough time to feel comfortable both before and after the blood collection. In many cases the most memorable part of the experience will be the contact with the technologist who draws the blood and his/her general attitude and competence.

- Handling participants who are extremely apprehensive about having blood drawn:
  - Do not under any circumstances force the participant to have blood drawn.
  - If the participant is nervous or excited, the technologist should briefly describe the procedure:
    - "I am going to be drawing about (number) tablespoons of blood. This blood will be used in tests for kidney function and other research analyses. We hope to be able to use the results of these tests to predict who might have a greater risk of kidney and heart disease."
  - Explain to the participant that the blood drawing is designed to be as nearly painless as possible. It is sometimes best to let the participant go on with another part of the visit.
  - Have the participant relax in the blood drawing chair just so the phlebotomist can check the veins in the participant's arms, without actually drawing blood.
  - If the participant has "good veins" the phlebotomist can reassuringly say, "Oh, you have good veins; there should be no problem."

4.B.7 Venipuncture Procedure

1. Preparation.
   - Remove all extra clothing and have the participant sit upright with the sleeves rolled up to expose the antecubital fossa (elbow).

- A tourniquet is used to increase venous filling. It makes the veins more prominent and easier to enter.

2. Precautions When Using a Tourniquet.
   - The tourniquet should be on the arm for the shortest time possible.
   - Never leave the tourniquet on for longer than two (2) minutes. To do so may result in hemoconcentration or a variation of blood test values.
   - If a tourniquet must be applied for the preliminary vein selection, it should be released and reapplied after a wait of two minutes.
   - If the participant has a skin problem, put the tourniquet over the participant's shirt or use a piece of gauze or paper tissue so as not to pinch the skin.
   - Wrap the tourniquet around the arm 3 to 4 inches (7.5 to 10.0 cm) above the venipuncture site.
   - Tuck the end of the tourniquet under the last round. If a Velcro tourniquet is used, adhere the ends to each other.
3. Identify the vein:
   - Palpate and trace the path of veins several times with the index finger. Thrombosed veins lack resilience, feel cord-like, and roll easily.
   - If superficial veins are not readily apparent, have the participant close his or her fist.
   - Lowering the extremity over the arm of the chair will allow the veins to fill to capacity.
   - Identify the best available vein.
4. Cleanse the venipuncture site.
   - Remove alcohol pad from its sterile package.
   - Cleanse the vein site with the alcohol pad using a circular motion from the center to the periphery.
   - Allow the area to dry to prevent possible hemolysis of the specimen and a burning sensation to the participant when the venipuncture is performed.
5. Assemble the butterfly-vacutainer set.
   - Attach the Luer adaptor to the vacutainer holder.
   - Attach the Luer end of the butterfly needle set to the Luer adaptor.
6. Perform venipuncture.
   - Grasp the participant's arm firmly, using your thumb to draw the skin taut. This anchors the vein. The thumb should be 1 or 2 inches (2.3 or 5.0 cm) below the venipuncture site.
   - With the needle bevel upward, enter the vein in a smooth continuous motion.
   - Make sure the participant's arm is in a flat or downward position while maintaining the tube below the site when the needle is in the vein. It may be helpful to have the participant make a fist with the opposite hand and place it under the elbow for support.
   - Grasp the flange of the needle holder and push the tube forward until the butt end of the needle punctures the stopper, exposing the full lumen of the needle.

- Start a timer to measure the flow rate of blood into the first blood collection tube. If the flow rate in the tube is so slow that blood does not fill the first collection tube within 50 seconds, stop the blood collection and repeat on the other arm. If blood is flowing freely, the butterfly tubing can be anchored to the participant's arm using medical tape for the duration of the draw.
- Remove the tourniquet after blood is flowing into the second tube.
- Keep a constant, slight forward pressure (in the direction of the needle) on the end of the tube. This prevents release of the shutoff valve and stopping of blood flow. Do not vary pressure nor reintroduce pressure after completion of the draw.
- Fill each vacutainer tube as completely as possible; i.e., until the vacuum is exhausted and blood flow ceases. If a vacutainer tube fills only partially, remove the vacutainer and attach another one without removing needle from vein.
- When the blood flow ceases, remove the tube from the holder. The shutoff valve recovers the point, stopping blood flow until the next tube is inserted.
- EDTA and ACD-A tubes should be gently mixed by inverting immediately after each tube is filled and removed from the butterfly setup.
- If it is not possible to collect all of the desired tubes, follow the requested order and fill each tube as completely as possible.

7. Prevent blood mixing during venipuncture.
   - Only invert tubes containing anticoagulant such as EDTA (purple top) and ACD-A (yellow top) collection tubes.
   - DO NOT SHAKE TUBES!!
   - To invert tubes, hold the tube horizontal to the floor.
   - Slowly tip the butt end down while watching the air bubble rise to the stopper (1st inversion).
   - When the bubble reaches the stopper, the tube should be at approximately a 22 degree angle to the floor.
   - Next lower the stopper while watching the bubble float to the butt end. Again the tube should be at a 22 degree angle to the floor (2nd inversion).
   - Lower the butt end again. This is the third inversion.
   - Invert each tube eight times. Eight inversions should take 13-15 seconds.
   - Proceed to 4.D., Processing.
8. If a blood sample is not forthcoming, the following manipulations may be helpful:
   - If there is a sucking sound, the tube has lost its vacuum. Replace with a new tube.
   - If no blood appears, move the needle slightly in hope of entering vein. Do Not Probe. If not successful, release tourniquet and remove needle. A second attempt can be made on the other arm.
   - The same technician should not attempt a venipuncture more than twice.
   - To remove the needle, lightly place clean gauze over venipuncture site. Remove the needle quickly and immediately apply pressure to the site with a gauze pad.

- Discard needle with its cap into a sharps container.

9. Bandage the arm.
   - Under normal conditions:
     - Slip the gauze pad down over the site, continuing mild pressure.
     - Apply an adhesive or gauze bandage over the venipuncture site after making sure blood flow has stopped.
   - If the participant continues to bleed:
     - Apply pressure to the site with a gauze pad. Keep the arm elevated until the bleeding stops.
     - Wrap the gauze bandage tightly around the arm over the pad.
     - Tell the participant to leave the bandage on for at least 15 minutes.
10. Precautions – If a participant feels faint or looks faint following the blood draw:
    - Have the person remain in the chair, if necessary have him/her sit with head between knees.
    - Take an ampule of smelling salts, crush it, and wave it under person's nose for a few seconds.
    - Provide the person with a basin if he/she feels nauseous.
    - Have the person stay reclined until their color returns and he/she feels better.
    - Place a cold wet cloth on the back of the person's neck.
    - If the person faints, use smelling salts to revive.
    - If the person continues to feel sick, take a blood pressure and pulse reading. Contact a medical staff member, who will advise you on further action.
11. Phlebotomy in pediatric participants should be performed by personnel with training and experience in obtaining blood from children. Subject positioning, reassurance methods and location of blood draw will be selected by experienced personnel. In addition:
    - The parents and/or child will already have signed consent to have blood drawn. However, they should be reminded of this prior to initiating preparations for blood draw. In addition, the DNA consent form must be signed for blood collection with the ACD-A tube.
    - Distraction techniques during the blood draw are encouraged.
    - For venipunctures, select the vein on an arm, hand or foot with the highest probability of venipuncture success.
    - For capillary blood specimen collection, it is recommended to apply a warm cloth for a few minutes to the area which will be punctured to increase local blood flow.
    - If anesthetic cream is being used, be sure to follow the instructions for the specific cream being used. Apply the cream at least 15 minutes prior to performing venipuncture or capillary blood collection. It is wise to select two spots for anesthetic cream application if venous access appears difficult. Be sure to clear the subject's arm of the anesthetic cream using water alone (not soap, which may irritate the skin) before venipuncture.
    - Assure that any parent or sibling in the room is seated.

- If venipuncture is unsuccessful after two attempts, ask permission to have another experienced personnel attempt to obtain the blood.

4.C Urine Collection

- If a diaper with cotton balls or urine collection bag is to be used for sample collection, begin the collection process at the start of the outpatient visit to maximize the likelihood of obtaining a specimen. Encourage parents/guardians to hydrate the participant prior to the visit with juice/milk/water. As noted below, if either the cotton ball or collection bag method is unsuccessful after two (2) hours with appropriate hydration, consider switching to the other method (e.g., collection bag -> diaper with cotton balls) as some participants may be able to void with one collection system in place but not the other, and vice versa.
- The urine samples should be aliquoted per date and time of collection. Refer to the Appendix for Charts E-H, J-M.
- Samples must be spun and frozen as quickly as possible (see Processing section), within six hours. If samples will not be processed within 30 minutes, place on ice immediately until the samples are spun, aliquoted and frozen.
- For the pediatrics visits, urinalysis should be performed if a clean catch void has been obtained but not on cotton ball or collection bag specimens.
- The mandatory minimum at Visit 3M and Visit 12M is 1.6mL for diaper-wearers and 5mL for non-diaper wearers.
- The only time that a urine sample may be collected by a participant at home and the participant may bring the urine sample to the visit is when the visit is an in-clinic visit, the urine was collected by straight catheter, and the urine was refrigerated or on ice/ice pack. All three conditions must be met. Indwelling Foley catheters are not included. This does not pertain to home visits. The Coordinator should email Georgia Brown Faulkner and copy ASSESS_DM to request a protocol exception and include the participant ID and confirm in writing that 1) visit was an in-clinic visit, 2) urine was collected by straight catheter, and 3) urine sample was refrigerated, on ice, or on ice pack. The site coordinator should make a note of this in the Comments section of the urine collection forms.

4.C.1 Clean Catch Void

Pediatric outpatients should do a clean catch void, if at all possible. Procedures for collecting a clean catch void are outlined below.

4.C.1.a Urine Collection Items

- Three special towelettes for midstream urine collection. Kaiser uses benzalkonium chloride towelettes.
- 5 oz wide mouthed cup for specimen collection

4.C.1.b Clean Catch Instructions for Males

1. Make sure your bladder is somewhat full.
2. Wash hands thoroughly with soap and water.
3. Retract the foreskin completely, if present.

4. Clean the end of the penis with special towelettes beginning at the urethral opening. Wipe in a circular motion AWAY from the opening.
5. Repeat the above procedure using two successive towelettes.
6. Void into toilet for a few seconds and then stop. Do NOT collect the first amount of urine. Restart urine stream and collect about ½ cup in the sterile container provided.
7. Void the remainder of urine into the toilet.
8. Cap and avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
9. Bring the container to the study personnel.

4.C.1.c Clean Catch Instructions for Females

"Clean catch" means that the urine sample is not contaminated with any vaginal discharge, menstrual blood, or bacteria. If you have vaginal discharge or are on your period, insert a fresh tampon into the vagina.

1. Wash hands thoroughly with soap and water.
2. Spread labia with 1 hand and hold apart for collection.
3. Use three special towelettes to clean area.
4. Wipe down one side, front to back, with one towelette
5. Wipe down other side, front to back, with second towelette
6. Wipe down center, front to back, with last towelette
7. Void into toilet for a few seconds and then stop. Do NOT collect the first amount of urine. Restart urine stream and collect about ½ cup in the sterile container provided.
8. Void the remainder of urine into the toilet.
9. Cap and avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
10. Bring the container to the study personnel.

4.C.2 Participants Unable to Perform a Clean Catch Void

If participant is spontaneously voiding but unable to perform a clean catch void due to physical constraints (weakness, deconditioning), collect urine as follows.

1. Do not have the participant use cleaning towelettes, as the cleaning agents in the towelettes may interfere with some sensitive bioassays.
2. Have the participant void into a urinal (men) or a clean hat on the toilet or on a commode (men or women)
3. Do not collect urine from a hat that is contaminated with stool
4. Study personnel should pour a small amount of urine into a labeled specimen cup.

5. Cap the container; avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.
6. Record that the urine was not a clean catch specimen in the comment section of the Pediatric Outpatient V3M Specimen Collection: Urine (P2_V3M_COLLECT_UA) form at V3M and the Pediatric Outpatient V12M Specimen Collection: Urine (/P2_V12M_COLLECT_UA) form at V12M and the Yearly Specimen Collection: Urine (P2_OUTPT_COLLECT_UA) at the annual visits (V24M, V36M, V48M, V60M, V72M, and V84M).

4.C.3 Cotton Balls Urine Collection (for Pediatric Sites) if Unable to Perform a Clean Catch Void

If the participant is wearing a diaper, the urine can be collected by inserting cotton balls in the diaper. Procedures for collecting urine from cotton balls are outlined below:

4.C.3.a Urine Collection Items

- Jumbo size cotton balls
- Plastic cling wrap of standard width (e.g. Saran Wrap)
- 5 oz wide mouthed cup for specimen collection

4.C.3.b Instructions for Cotton Ball Urine Collection

1. Prepare the collection cup containing the cotton balls:
   - Cut-out a piece of plastic wrap (approximately 7 inches in length).
   - Place 3 to 4 jumbo sized cotton balls in the center of the plastic wrap (number of cotton balls to be used is dependent on the size of the patient: for infants use three (3) cotton balls and for young children use four (4) cotton balls). Gently enclose the corners of the plastic wrap over the cotton balls.
   - Place the plastic wrapped cotton balls in the specimen collection container.
2. Bring the collection cup to the bedside nurse or legal guardian and explain the procedure of inserting the cotton balls into the diaper (see Figure 4.3 below for a schematic view of the procedure):
   - Remove the plastic-wrapped cotton balls from collection cup
   - In a new diaper, unwrap the cotton balls by ensuring to keep the cotton balls centered and on top of the plastic wrap.
   - Put diaper on patient as usual, and ensure the alignment of the cotton balls to the area of urine collection in the diaper (i.e. centered for female patients and towards the front of the diaper for male patients).
   - Ask the legal guardian or nurse to check the diaper regularly to avoid fecal contamination of the cotton balls.
   - To remove the cotton balls, simply re-wrap the cotton balls in the plastic wrap and place in the collection cup.

- If no urine is produced by the cotton ball method after two (2) hours, consider applying a urine collection bag for sample collection (some participants will be able to void into the bag but not into the diaper, and vice versa).

3. To extract urine from the cotton ball, simply squeeze the cotton balls into the collection cup, either manually (always wear gloves) or by using a needleless syringe.

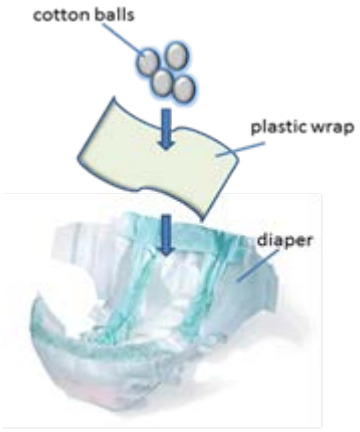


Figure 4.3. Diagram illustrating the insertion of cotton balls in a diaper for urine collection

4.C.4 Collection Bag Urine Collection (for pediatric sites) If Unable to Perform a Clean Catch Void

If the pediatric subject is not wearing a diaper but cannot provide a clean catch void, then a urine collection bag may be used to obtain urine.

4.C.4.a Urine Collection Items

- Sterile urine collection bag
- Cotton cloth moistened with water
- Dry cotton cloth
- Sterile 10cc syringe

1. With the aid of the parent or guardian, encourage the subject to drink.
2. Ask the parent or guardian to gently wipe the vaginal area from front to back (girls) or the gently wipe the tip of the penis (boys). For boys, do not force retraction of the foreskin.
3. Gently wipe the area which will be covered by the urine collection bag with the moist cloth. If the area of the skin where the bag will be stuck is significantly irritated, either place a gauze pad on that area to avoid bag-skin contact (if very localized irritation) or abort use of the urine collection bag.

4. Gently pat-dry the area of skin where the urine collection bag will be taped.
5. Firmly apply the urine collection bag to the area, making sure that there is as good a seal as possible between the bag and the skin. For girls, the vulvar area should be completely covered and for boys, the lower portion of the bag should be stuck on just below the testes (avoid the anal region).
6. Once voiding has occurred, gently remove the bag. If no urine is produced by the urine collection bag method after 2 hours, consider putting on a diaper with cotton balls for sample collection (some participants will be able to void into the diaper but not the bag, and vice versa).
7. Using the sterile 10cc syringe, draw out the urine from the bag, avoiding contamination and transfer the urine to the designated urine collection cup.

4.C.5 Urine Sample Prioritization

If the sample is 1.6mL of a diaper-wearer, the sample should be prioritized as follows:

- One 0.6mL aliquot for the Central Lab
- One 1.0mL aliquot to the NIDDK Biorepository
- If the sample is less than 10cc, the sample should be prioritized as follows:
  - First 5cc: Aliquots for the Central Lab and NIDDK Biorepository. Urine should be aliquoted as 1mL aliquots.
  - If between 5 and 10cc is available, make at least 5 x 1mL aliquots. Perform urine analysis with Bayer Clinitek Status Analyzer as below.

4.C.6 Urine Analysis

Urine analysis will be performed using the Bayer Clinitek Status Analyzer by the research coordinators. This is suggested for pediatric participants in whom a clean catch void was obtained. For home visits, urine analysis will be done at the Clinical Research Center, not in the participants' home.

- If more than 30cc or urine were collected:

1. Pour approximately 5cc of urine into a 10 or 15mL conical tube
2. Dip the test strip into the urine quickly, ensuring all pads are soaked
3. Place test strip into analyzer. You will have eight (8) seconds to do this from the time you hit 'Start' on the analyzer.

- If less than 30cc of urine were collected:

1. Use a soft bulb pipette to aspirate up 1-2mL of urine
2. Quickly pipette one (1) drop onto each pad of the stick, ensuring that all pads are soaked
3. Place test strip into analyzer. You will have eight (8) seconds to do this from the time you hit 'Start' on the analyzer.

4.D Processing

The processing of specimens should be completed within six hours of collection and preferably within 2.5 hours, if possible, with the exception of blood collected for Rutgers (Precision for Medicine after March 2018) in an ACD-A tube that is kept at room temperature and is not processed. Blood collected in EDTA tubes and urine biospecimens should be stored on ice or refrigerated until processed. Follow the instructions below to centrifuge and aliquot the blood and urine specimens for the inpatient visit. If samples will not be processed within 2.5 hours (from the time that the blood is drawn until processing is started), serum samples are to be processed in the field using battery operated centrifuges. Plasma and urine tubes will be spun and processed at the Clinical Center Laboratory, with the exception of blood collected in an ACD-A tube at V12M that is kept at room temperature and is shipped unprocessed to Rutgers (Precision for Medicine after March 2018).

4.D.1 Gather Equipment and Supplies

- Centrifuge
- Transfer pipettes
- Aliquot rack
- Room temperature test tube rack to hold the collected V12M ACD-A citrate tube at room temperature until shipment to Rutgers (Precision for Medicine after March 2018)
- 15 2mL cryovials (10 for urine, five (5) for blood), one additional 2mL cryovial for any remaining blood, and two 10mL cryovial (urine) for any remaining urine.
- Cap inserts (red for blood aliquots, yellow for urine aliquots) are provided for the Clinical Research center. Use of the colored inserts is not mandatory.
- 15mL or 50mL conical tubes for centrifugation
- Balance tubes for centrifugation
- Waste disposal containers and sharps container
- Cardboard freezer and transport boxes
- Freezer at -80ºC
- Safety: Obtain and utilize necessary protective clothing/equipment for preparing an aliquot of specimens. Such items include but are not limited to lab coats, gloves, protective eyewear, and absorbent pads.

4.D.2 Safety Precautions for Handling Blood and Urine Specimens

- All specimens are handled as potentially infectious for laboratory workers. Transmissions of the infectious agents associated with Hepatitis and HIV via “needle stick” skin punctures have been documented.
- Where feasible, wear disposable plastic gloves when collecting and processing specimens. Alternatively, wash hands thoroughly with disinfectant soap prior to leaving the work area. Skin cuts or abrasions should be covered.

- Aliquot/process specimens within a biological safety cabinet
- Use 0.1% sodium hypochlorite (household bleach) to clean up any spills of blood, plasma, or serum. Use this solution to clean up all laboratory work surfaces at the completion of work activities.
- Dispose of all needles and tubing in puncture-resistant sharps containers for safe disposal.
- Do not perform any pipetting by mouth.
- Avoid formation of potentially infectious aerosols by careful pipetting and centrifugation.
- All used vacutainers tubes, needles, and blood products are to be placed in spill proof liquid biohazard sharps containers for disposal.

4.D.3 Centrifuge Instructions

1. Separate and sort any specimens that are not centrifuged (i.e. DNA samples or samples to be sent directly to the local lab).
2. Allow serum samples to clot for at least 30 minutes prior to processing.
3. Balancing the centrifuge ensures proper performance of the instrument. Determine the amount of sample volume in each tube and find another tube filled to approximately the same level to ensure correct balancing.
4. Use a "balance tube" filled with water to the proper level if there are an uneven number of specimens
5. After pairing the tubes by their sample volume, place them into the centrifuge using the following guidelines:
    - If the centrifuge contains buckets, position the tubes in the buckets so that the tube and its match are located in opposite buckets (mirror image of each other). Select holes in the opposing buckets that allow for equal weight distribution. See Figure 4.4.
    - Once the centrifuge is loaded with samples, set the speed for 1000 g, and time for 10 minutes. Start the centrifuge. At Vanderbilt, Kaiser and Yale-New Haven, centrifuge is set at 4 degrees for processing. At other Yale sites, centrifuge is set at room temperature for processing.
    - Once the centrifuge is stopped, open the centrifuge and remove the specimens.
    - Locate and arrange the specimens by participant to keep each set of specimens and aliquots organized.
    - Aliquot and freeze all biospecimens.
    - If a urine specimen did not pellet properly, go ahead and aliquot and freeze the biospecimen. Do not re-centrifuge. Add this to the comments section (6000) of the Inpatient Specimen Collection Form.
    - If a blood specimen did not pellet properly, respin at 2000 g for 15 minutes, ideally in a refrigerated centrifuge. Add this to the comments section (6000) of the Inpatient Specimen Collection Form.

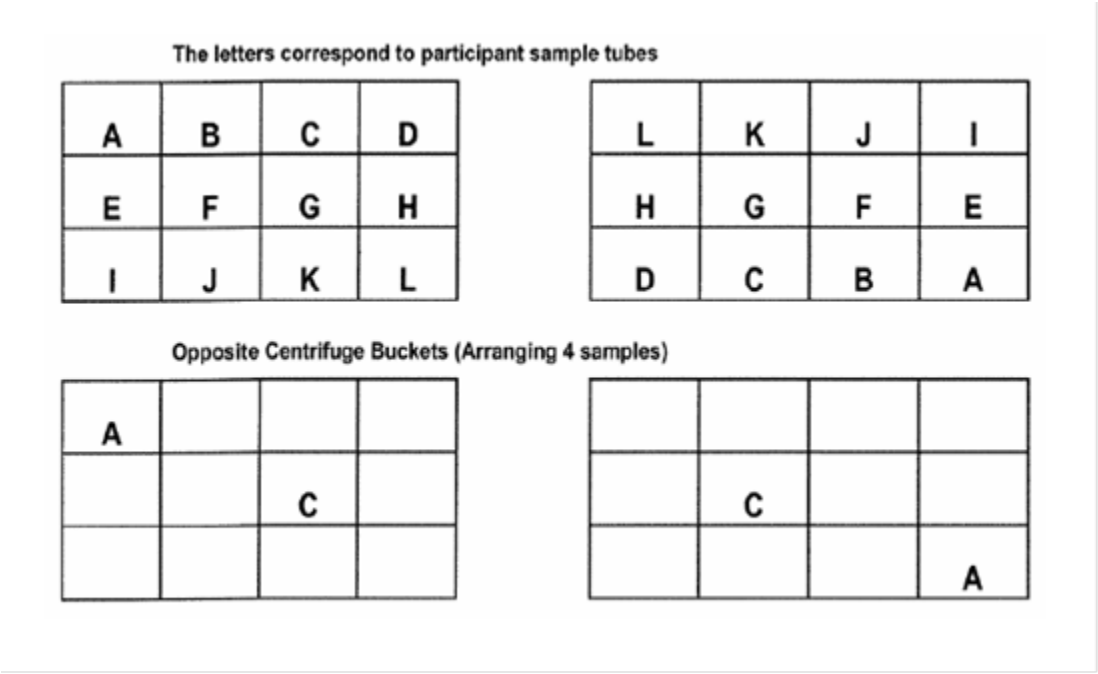


Figure 4.4. Centrifuge Bucket

4.D.4 Create Barcode Labels

The barcode labels will be printed by the individual sites. If additional barcode labels are necessary or if there are problems printing labels at the site, allow a five work day window for the DCC to generate and ship labels to the sites.

1. The sites will access the Barcodes link on the main website under Direct Module Access or within the specified protocol (2-peds).
2. In the Barcode Label Generator screen, the protocol number and center number will populate with the correct information.
3. Select a Print Type of New if this is a new sheet of labels or Re-Print if you are reprinting a label sheet that has already been generated.
4. Select a Print Duplicates with option 'Yes' if the user wants a duplicate page to be printed for the URINE_LOG and BLOOD_LOG forms.
5. Once the information is entered, select Generate Labels.
6. A .cfm page will appear in Adobe .pdf format where the labels will populate one sheet of labels for one participant at the Visit.
    - Adobe upgrades can affect the label printing.
    - Sites have reported labels printing offline and therefore labels are wasted.
    - Whenever you have upgrades at your site, please print the labels on a blank piece of paper to make sure that alignment is still good.

- If you find that the alignment is off, you can adjust the settings on the print preview screen and print again.
- The most common default on the print preview screen is 'actual size' however this may no longer work when upgrades are distributed for Adobe. Try 'fit' and 'shrink oversized pages'. Either of these settings should allow the labels to align and print correctly on the label sheet.

7. Place the blank label sheet in the laser jet printer face down and print the labels.
8. One label sheet will be printed for each participant along with a P2_V3M_URINE_LOG, P2_V3M_BLOOD_LOG, P2_VXXM_URINE_LOG, and P2_VXXM_BLOOD_LOG (for pediatric participants).

4.D.5 Prepare an Aliquot Sample

- Aliquot samples are necessary any time the original specimen collection tube or container cannot be used for storing the specimen.
- Verify that the specimens have been properly centrifuged and cells have been clearly separated.
- Use a disposable transfer pipette to transfer the sample from the primary tube to the appropriately labeled secondary tubes, in this case 2mL cryovials.
- When removing plasma or serum using a transfer pipette, be very careful not to disturb the buffy coat (white cell layer) or the serum separator layer.
- Store all aliquots in a plastic rack or cardboard freezer box in an upright position at -80°C immediately. Label the racks or cardboard boxes with permanent marker or an adhesive label that say "ASSESS-AKI Outpatient Biospecimens."

4.D.6 Aliquot Instructions for Outpatient Pediatric Visits

Before aliquoting, affix all barcoded labels lengthwise on the tube for ease of scanning at the sites and the NIDDK Biorepository/central lab/other partner laboratories. It is required to affix the clear adhesive label over the barcode label while overlapping the ends of the clear adhesive label. Make sure that the label does not overlap on top of the barcode because that may interfere with scanning the barcode.

4.D.6.a General Instructions

- Red inserts for the cap of the blood specimen aliquots and yellow inserts for the caps of the urine specimen aliquots are provided. Use of the colored inserts is not mandatory.
- Using a pipette, transfer the supernatants to the 2mL aliquot tubes provided.
- Be careful not to disrupt any cellular debris at the bottom of the tube.

4.D.6.b EDTA Plasma (Purple Top) Instructions

1. Place tubes into the centrifuge and spin for ten minutes at 1000 g as soon as possible after collection.

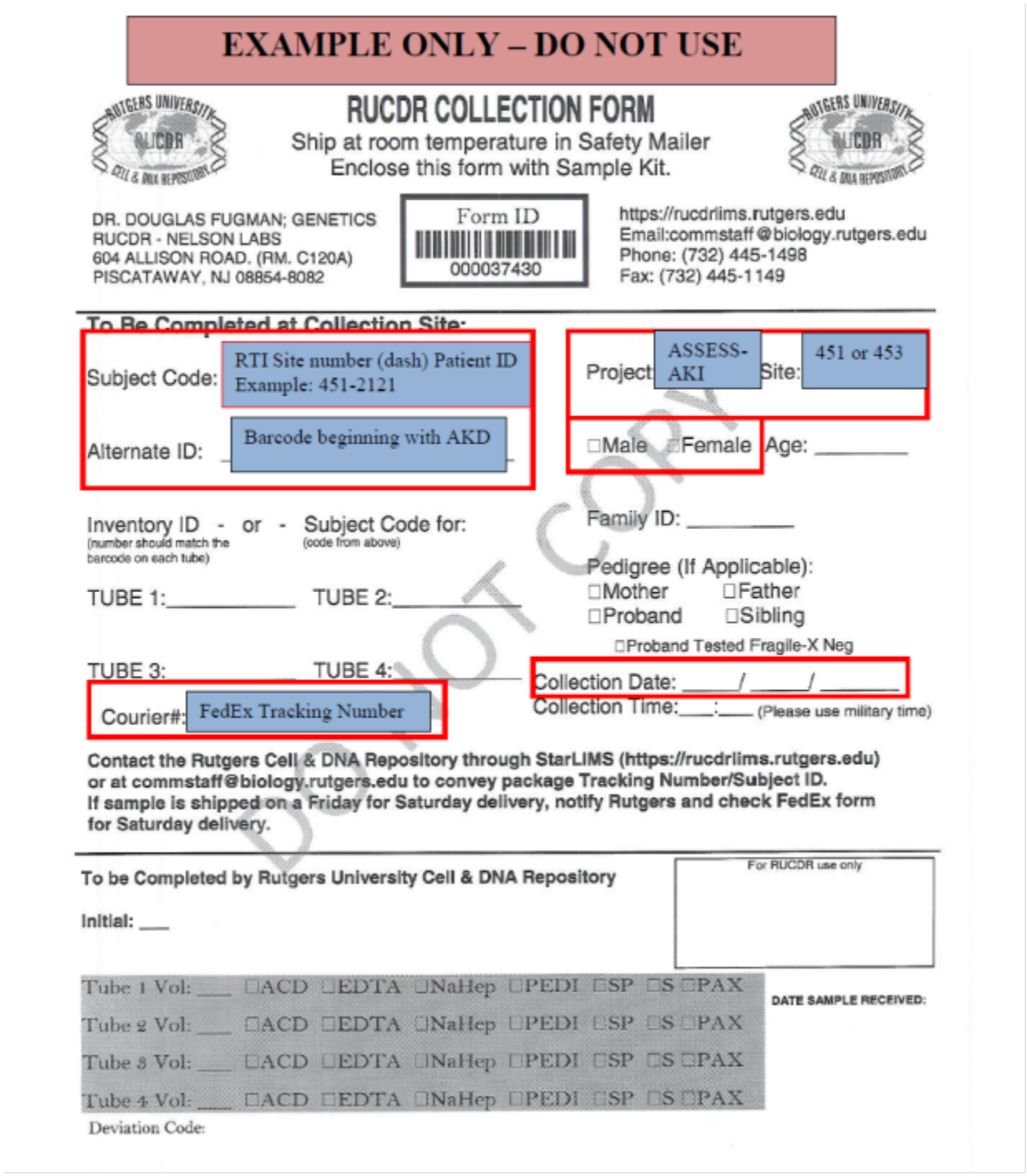
2. Pipet 0.5mL of plasma into one barcode-labeled 2mL cryovial and 0.25mL of plasma into the remaining four (4) cryovials. It is OK to under fill the last aliquot for pediatric samples ONLY.
3. Any leftover plasma after aliquoting should be transferred to a 6th 2mL cryovial.
4. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST).
5. Put the cryovials for the Central Lab into a labeled box and place them into the freezer for weekly shipment.
6. Put the cryovials for the NIDDK Biorepository into a labeled box and place them into the freezer for monthly shipment.

4.D.6.c Collection Logs for Blood Aliquots

1. Affix the duplicate barcode label for each sample on the P2_V3M_BLOOD_LOG, P2_V12M_BLOOD_LOG, or P2_VXXM_BLOOD_LOG for each participant by sample type and aliquot number.
2. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST) using the P2_V3M_BLOOD_LOG, P2_V12M_BLOOD_LOG, or P2_VXXM_BLOOD_LOG

4.D.6.d ACD-A Citrate (Yellow Top) Instructions

- The ACD-A tubes are to be kept at room temperature at all times and sent unprocessed on the day of collection, when possible, to Rutgers for shipments prior to November 2017 (for shipment time windows, please see below).
- Complete and attach ID labels to the tubes making sure the label does not cover the barcode on the tube. DO NOT write the patient's name or any other personal identification information (e.g. SS#, DOB) on the tubes.
- Collect blood specimen in the yellow top (ACD) tube provided. Be sure to invert the tube gently 8 to 10 times to mix blood with additives and keep the tube at room temperature.
- On the RUCDR Collection Form fill in the following fields:
    a. Subject Code – RTI site number (451 or 453), followed by a hyphen and then the -Participant ID number (four digit number from the label printed by the coordinator), example: 451-2121, pediatric participant at Cincinnati site or 453-1111, pediatric participant at Montreal site)
    b. Alternate ID – Barcode from the label printed by the coordinator beginning with AKD
    c. Inventory ID – Barcode that is already on the tubes when they are received
    d. Collection Date
    e. Project – ASSESS-AKI
    f. Site – NIDDK site number (Cincinnati enter 451, Montreal enter 453)
    g. Sex/Age
    h. Family ID and Pedigree – leave blank
    i. Courier # - tracking number for package



EXAMPLE ONLY – DO NOT USE

RUCDR COLLECTION FORM

Ship at room temperature in Safety Mailer
Enclose this form with Sample Kit.

DR. DOUGLAS FUGMAN; GENETICS
RUCDR - NELSON LABS
604 ALLISON ROAD. (RM. C120A)
PISCATAWAY, NJ 08854-8082

Form ID
000037430

https://rucdrlims.rutgers.edu
Email:commstaff@biology.rutgers.edu
Phone: (732) 445-1498
Fax: (732) 445-1149

To Be Completed at Collection Site:

Subject Code: RTI Site number (dash) Patient ID Example: 451-2121

Alternate ID: Barcode beginning with AKD

Project: ASSESS-AKI Site: 451 or 453

☐Male ☐Female Age: _____

Inventory ID - or - Subject Code for:
(number should match the barcode on each tube) (code from above)

TUBE 1:_____ TUBE 2:_____

TUBE 3:_____ TUBE 4:_____

Courier#: FedEx Tracking Number

Family ID: _____

Pedigree (If Applicable):
☐Mother ☐Father
☐Proband ☐Sibling
☐Proband Tested Fragile-X Neg

Collection Date: ____/____/_____
Collection Time:___:___ (Please use military time)

DO NOT COPY

Contact the Rutgers Cell & DNA Repository through StarLIMS (https://rucdrlims.rutgers.edu) or at commstaff@biology.rutgers.edu to convey package Tracking Number/Subject ID.
If sample is shipped on a Friday for Saturday delivery, notify Rutgers and check FedEx form for Saturday delivery.

To be Completed by Rutgers University Cell & DNA Repository

Initial: ___

For RUCDR use only

Tube 1 Vol: ___ ☐ACD ☐EDTA ☐NaHep ☐PEDI ☐SP ☐S ☐PAX
Tube 2 Vol: ___ ☐ACD ☐EDTA ☐NaHep ☐PEDI ☐SP ☐S ☐PAX
Tube 3 Vol: ___ ☐ACD ☐EDTA ☐NaHep ☐PEDI ☐SP ☐S ☐PAX
Tube 4 Vol: ___ ☐ACD ☐EDTA ☐NaHep ☐PEDI ☐SP ☐S ☐PAX

DATE SAMPLE RECEIVED:

Deviation Code:

- Double check that the ID information on tube matches that on the RUCDR Collection Form.
- Please notify Rutgers University Cell and DNA Repository that you are shipping the sample by logging into STARLIMS at the following website http://www.rucdr.org/lims.htm. (Precision for Medicine after March 2018)
- On left-hand side menu bar, click on User Login

- A new window opens prompting for user name and password. These were provided by Rutgers. Enter these and click ok. (If there are multiple members at one site, ensure to properly select options for site and role- these fields appear once the user name is entered). * Upon first login, user will be prompted to reset a new password.
- Once logged-in, the window has three (3) panels. Click Sample Submission in the right panel, under Login Options.
- Complete the following information under "Step 1" in the upper part of the window:
  - Submitter: field is auto-filled with username
  - Project: Choose NIDDK ASSESS-AKI (NIDDK) from the pull-down menu
  - Site: Choose your site from the pull-down menu (451 for Cincinnati, 453 for Montreal)
  - Courier: Choose FedEx from the pull-down menu
- Complete the following under "Step 2" in the lower part of the window:
  - Click "Manually add samples to the list"
  - A new window opens. In the left-hand side of the window, under "Details", complete the following (the information to be filled out in this section is obtained from the RUCDR Collection Form):
    - Form #: Form ID. Found on the top of the RUCDR Collection Form. Type-in the numbers written under the barcode.
    - Subject ID: RTI site number (451 or 453), followed by a hyphen and then the -Participant ID number (four digit number from the label printed by the coordinator)
    - Alternate ID: Barcode from the label printed by the coordinator beginning with AKD
    - Family ID: keep blank
    - Pedigree: keep blank
    - Sex: enter gender of participant
    - Age: this is optional
    - Date collected: choose collection date from the pull-down menu
    - Review the data entered to ensure that proper information has been entered.
  - In the right-hand side of the window, under "Samples", complete the following:
    - Source: it is automatically prompted to WB (whole blood). Leave this as is.
    - Inventory ID: scan the barcode found on the ACD tube (DO NOT SCAN THE ASSESS-AKI PARTICIPANT BARCODE LABEL)
    - Click "Add"
    - Once all the samples for the participant have been entered click "Save"
    - Once all the samples for the shipment have been entered, click in the upper right corner "Submit Request"

It is important to note that each RUCDR Collection Form corresponds to ONE PARTICIPANT. If multiple ACD tubes were collected for multiple participants in one day, a RUCDR Collection Form must be completed for each participant. Each form will contain ACD tube collection information for one specific participant. A shipment may contain samples from multiple participants. Each form is entered in STRALIMS by simply clicking "Manually add Samples to the list" where you will be prompted for the new Form ID and Subject Code.

V12M ACD-A tubes must be shipped to Rutgers (Precision for Medicine after March 2018) on the same day of sample collection. If visit occurred in the evening and same day shipment is not possible, prioritize next day morning shipment. If weekend shipments cannot be accommodated, please avoid Friday evening and weekend V12M visits. In addition, the holiday schedule must be considered when scheduling a blood collection for a DNA sample to be sent to Rutgers (Precision for Medicine after March 2018). Please refer to the Holiday Closure Table in Section 5.D for greater details on operating hours. Under certain circumstances, ACD-A tubes must be received by Rutgers (Precision for Medicine after March 2018) within 4 days from the time of collection. If this is not possible, the study visit should be rescheduled to ensure proper shipment.

- Call Federal Express (1-800-GO-FEDEX) to schedule a pick-up. Be sure to give FedEx the zip code of the pickup address, not that of the destination. Do not put mailer in a FedEx drop box.
- Pack the tubes in the kit using the directions in Section 5.D.

4.D.6.e Urine Instructions

1. Place the spot urine collection in one or two 15 or 50mL conical vial labeled with the participant's ID, depending on the sample volume.
2. Centrifuge for 10 minutes at 1000 g.
3. Pipet 1mL of supernatant into each barcode-labeled 2mL cryovial.
4. Fill as many of the 10 cryovials as possible. Vials should be filled with exactly 1.0mL. It is OK to under fill the last cryovial for pediatrics participants only
5. One aliquot should be sent to the Central Lab. All other urine aliquots will be shipped to the NIDDK Biorepository.
6. If there is leftover urine after the 10 x 1mL aliquots are filled, the remaining urine should be transferred to one 10mL cryovial. If there is more than 10mL of urine, another 10mL cryovial may be used.
7. Any leftover urine after aliquoting is completed may be discarded or stored at Clinical Research Center.
8. Affix the duplicate barcode label for each sample on the P2_ V3M_URINE_LOG, P2_V12M_URINE_LOG, or P2_VXXM_URINE_LOG for each participant by sample type and aliquot number.
9. Scan samples into ASSESS-AKI Biological Sample Tracking system (BST) using the P2_ V3M_URINE_LOG, P2_V12M_URINE_LOG, or P2_VXXM_URINE_LOG.
10. Put the cryovials for the Central Lab into a labeled box and place them into the freezer for weekly shipment.

11. Put the cryovials for the NIDDK Biorepository into a labeled box and place them into the freezer for monthly shipment.
12. Any remaining urine can be discarded.

4.E Visit 3M Forms: PEDIATRICS

4.E.1 P2_V3M_COLLECT_BLD

- Complete the Visit Date as the current date the Pediatric Outpatient V3M Specimen Collection: Blood (P2_V3M_COLLECT_BLD) form is completed.
- Q1000. This question is completed for home visits only to indicate if extra time will be allowed between collection and processing.
- Q1010. Record the date of the blood draw. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1020. Record the time blood specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1030. Was a blood sample collected?
  - IF NO, reschedule another collection within 48 hours of this collection and complete the Outpatient V3M Specimen 2+ Collection: Blood (P2_V3M_COLLECT_BLD_2) form.
  - IF NO, and another collection cannot be completed within the 48-hour period, reschedule another V3M within the visit window.
  - IF NO, and another collection cannot be scheduled within the 48-hour period and another V3M cannot be completed within the visit window, stop here. Plasma samples will not be entered into the BST as not collected.
- Q1040. Record the method used to collect the blood specimen.
- Q1050. Record if the EDTA purple top vacutainer was collected.
- Complete the site specific worksheet.
- If another collection is successfully completed within 48 hours of the initial collection, complete the V3M Specimen 2+ Collection: Blood (P2_V3M_COLLECT_BLD_2) form.
  - The 2+ forms should only be entered into the database when the last collection attempt is completed within the 48-hour period.
  - The 2+ forms are entered into the database as single forms.
- If another collection is completed within the V3M visit window, the forms completed at the rescheduled visit will be used for entry into the database and should be sent to the DCC.
  - The original V3M forms can be stored at the site.

4.E.2 P2_V3M_COLLECT_UA

- Complete the Visit Date as the current date the Pediatric Outpatient V3M Specimen Collection: Urine (P2_V3M_COLLECT_UA) form is completed.
- Q1000. This question is completed for home visits only to indicate if extra time will be allowed between collection and processing.

- Q1020. Record the date of the urine collection. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1030. Record the time urine specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1035. Record if the participant is wearing a diaper.
- NOTE: If a participant collects a urine sample at home and brings it to the visit, enter the date sample collected by the participant in Q1020, the time sample collected by the participant in Q1030, and answer Q1035 regarding the participant's diaper-wearing status. Q1040 should be left missing for samples collected at home by the participant.
- Q1040. Record the method used to collect the urine sample.
- Q1050. Was the minimum amount of urine collected? Minimum for DIAPER WEARERS is 1.6mL and the minimum for NON-DIAPER WEARERS is 5mL.
    - IF NO, reschedule another collection within 48 hours of this collection and complete the V3M Specimen 2+ Collection: Urine (P2_V3M_COLLECT_UA_2) form.
    - IF NO, and another collection cannot be completed within the 48-hour period, reschedule another V3M within the visit window.
    - IF NO, and another collection cannot be scheduled within the 48-hour period and another V3M cannot be completed within the visit window, stop and complete the ASSESS-AKI Withdrawal (WITHDR) form.
- Complete the site specific worksheet.
- If another collection is successfully completed within 48 hours of the initial collection, complete the V3M Specimen 2+ Collection: Urine (P2_V3M_COLLECT_UA_2) form.
    - The 2+ forms should only be entered into the database when the last collection attempt is completed within the 48-hour period.
    - The 2+ forms are entered into the database as single forms.
- If another collection is completed within the V3M visit window, the forms completed at the rescheduled visit will be used for entry into the database and should be sent to the DCC.
    - The original V3M forms can be stored at the site.

4.E.3 P2_V3M_PROCESS

- Complete the Visit Date as the current date the Pediatric Outpatient V3M Specimen Processing (P2_V3M_PROCESS) form is completed.
- Q995. Record and enter the sample collection date into the database. This is an additional field included on the Pediatric Outpatient V3M Specimen 2+ Processing (P2_V3M_PROCESS_2) form.

4.E.3.a Blood Specimen Processing

- Q1000. If there are no blood samples to be processed, complete the site specific worksheet and proceed to Question 1080.
- Q1010. Record the number of 0.5ml aliquots of serum produced from the EDTA purple top tube or capillary tube. The ASSESS-AKI goal is 1 (0.5ml aliquot).
- Q1020. Record the number of 0.25 ml aliquots of plasma produced from the EDTA purple top tube or capillary tube. The ASSESS-AKI goal is 4 (0.25ml aliquots).
- Q1040. Record if an extra aliquot was produced.
- Q1050. If there is an additional aliquot, estimate the amount of plasma saved and report to the nearest hundredth ml.
- Q1060. Record the date the aliquots were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1070. Record the time aliquots were frozen using a 24-hour clock. Aliquots should be stored in a --80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.

4.E.3.b Urine Specimen Processing

- Q1080. If there are no urine samples to be processed, complete the site specific worksheet and proceed to the Biological Sample Tracking module and enter all urine records as not collected.
- Q1090. Record the number of 1.0ml aliquots of urine produced. The ASSESS-AKI goal is 10 (1.0 mL aliquots).
- Q1095. Record if an extra aliquot of urine (less than 1.0mL) was produced. To be completed only if the participant wears diapers.
- Q1100. Record the number of 10ml aliquots of urine produced. The ASSESS-AKI goal is 1 (10mL aliquot).
- Q1110. Record if an extra aliquot of urine (less than 10mL) was produced.
- Q1120. Record the date the aliquots were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1130. Record the time aliquots were frozen using a 24-hour clock. Aliquots should be stored in a --80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- If you need to process/spin the blood or urine samples a second time, include a comment in Q6000.
- If multiple collection attempts are made, complete the V3M Specimen Processing 2+ (P2_V3M_PROCESS_2) form(s).
- When the LAST collection attempt has been completed for the visit, enter all appropriate samples into the Biological Sample Tracking module.

4.E.4 P2_V3M_BLOOD_LOG

- At Visit 3M, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- If multiple collection attempts are completed within the 48-hour period or within the outpatient visit window, multiple logs should be used.
  - Complete one log for each collection date.
  - Use the logs when entering the urine samples into the BST.
- This log will be stored at the clinical center and should not be sent to the DCC.
- This log will be reviewed during ASSESS-AKI site visits.

4.E.5 P2_V3M_URINE_LOG

- At Visit 3M, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- If multiple collection attempts are completed within the 48-hour period or within the outpatient visit window, multiple logs should be used.
  - Complete one log for each collection date.
  - Use the logs when entering the blood samples into the BST.
- This log will be stored at the clinical center and should not be sent to the DCC.
- This log will be reviewed during ASSESS-AKI site visits.

4.E.6 P2_V3M_SAMPLE PRIORITY

- This form serves as a guide to the Research Coordinator in collecting and shipping the blood and urine samples in order of priority. Please collect and ship the samples following the priority order outlined on the checklist.
- This form is not entered during data entry and should not be sent to the DCC.

4.F Visit 12M Forms: PEDIATRICS

4.F.1 P2_V12M_COLLECT_BLD

- Complete the Visit Date as the current date the Pediatric Outpatient V12M Specimen Collection: Blood (P2_V12M_COLLECT_BLD) form is completed.
- Q1000. This question is completed for home visits only to indicate if extra time will be allowed between collection and processing.
- Q1010. Record the date of the blood draw. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1020. Record the time blood specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1030. Record if the minimum amount (0.175 mL) of plasma was collected.
  - IF NO, reschedule another collection within 48 hours of this collection and complete the Pediatric Outpatient V12M Specimen 2+ Collection:Blood (P2_V12M_COLLECT_BLD_2) form.
  - IF NO, and another collection cannot be completed within the 48-hour period, reschedule another V12M within the visit window.
  - IF NO, and another collection cannot be scheduled within the 48-hour period and another V12M cannot be completed within the visit window, stop here and complete the ASSESS-AKI WITHDRAWAL (WITHDR) form.
- Q1040. Record the method of blood collection ONLY IF BLOOD SAMPLE WAS COLLECTED.
- Q1050. Record if the EDTA purple top vacutainer was collected.
- Q1060. Record if the ACD-A citrate yellow top vacutainer was collected with the 3mL blood for DNA.
- IF DNA samples were not collected, prepare to attempt the DNA blood draw at the V24M visit.
- Complete the site specific worksheet.
- If another collection is successfully completed within 48 hours of the initial collection, complete the V12M Specimen 2+ Collection:Blood (P2_V12M_COLLECT_BLD_2) form.
  - The 2+ forms should only be entered into the database when the last collection attempt is completed within the 48-hour period.
  - The 2+ forms are entered into the database as single forms.
- If another collection is completed within the V12M visit window, the forms completed at the rescheduled visit will be used for entry into the database and should be sent to the DCC.
  - The original V12M forms can be stored at the site.

4.F.2 P2_V12M_COLLECT_UA

- Complete the Visit Date as the current date the Pediatric Outpatient V12M Specimen Collection: Urine (P2_V12M_COLLECT_UA) form is completed.
- Q1000. This question is completed for home visits only to indicate if extra time will be allowed between collection and processing.
- Q1020. Record the date of the urine collection. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1030. Record the time urine specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1035. Record if the participant is wearing a diaper.
- NOTE: If a participant collects a urine sample at home and brings it to the visit, enter the date sample collected by the participant in Q1020, the time sample collected by the participant in Q1030, and answer Q1035 regarding the participant's diaper-wearing status. Q1040 should be left missing for samples collected at home by the participant.
- Q1040. Record the method used to collect the urine sample.
- Q1050. Was the minimum amount of urine collected? Minimum for DIAPER WEARERS is 1.6mL and the minimum for NON-DIAPER WEARERS is 5mL.
    - IF NO, reschedule another collection within 48 hours of this collection and complete the Pediatric Outpatient V12M Specimen 2+ Collection:Urine (P2_V12M_COLLECT_UA_2) form.
    - IF NO, and another collection cannot be completed within the 48-hour period, reschedule another V12M within the visit window.
    - IF NO, and another collection cannot be scheduled within the 48-hour period and another V12M cannot be completed within the visit window, stop and complete the ASSESS-AKI Withdrawal (WITHDR) form.
- Complete the site specific worksheet.
- If another collection is successfully completed within 48 hours of the initial collection, complete the Pediatric Outpatient V12M Specimen 2+ Collection:Urine (P2_V12M_COLLECT_UA_2) form.
    - The 2+ forms should only be entered into the database when the last collection attempt is completed within the 48-hour period.
    - The 2+ forms are entered into the database as single forms.
- If another collection is completed within the V12M visit window, the forms completed at the rescheduled visit will be used for entry into the database and should be sent to the DCC.
    - The original V12M forms can be stored at the site.

4.F.3 P2_V12M_PROCESS

- Complete the Visit Date as the current date the Pediatric Outpatient V12M Specimen Processing (P2_V12M_PROCESS) form is completed.

- Q995. Record and enter the sample collection date into the database. This is an additional field included on the Pediatric Outpatient V12M Specimen 2+ Processing (P2_V12M_PROCESS_2) form.

4.F.3.a Blood Specimen Processing

- Q1000. If there are no blood samples to be processed, complete the site specific worksheet and proceed to Question 1100.
- Q1010. Was the collected amount less than or equal to the minimum of 0.175mL of plasma?
  - IF MORE THAN THE MINIMUM WAS COLLECTED, PROCEED TO Q3 and skip Q2a & 2b.
  - If the response to Q1010 is YES, answer Q2a & Q2b and then proceed to Q6.
- Q1020. Record if there is a 0.150mL aliquot.
- Q1030. Record if there is a 0.025mL aliquot.
- Q1040. Record the number of 0.5mL aliquots of serum produced from the EDTA purple top tube or capillary tubes. The ASSESS-AKI goal is 1 (0.5mL aliquot). If more than the minimum amount (0.175mL) of plasma were collected, but the goal amount (0.5mL) of plasma was not reached, one 0.150mL aliquot should be prepared for the Central Lab to evaluate sCr and Cystatin C. Q1040 should be answered 1 in this case.
- Q1050. Record the number of 0.25ml aliquots of plasma produced from the EDTA purple top tube or capillary tubes. The ASSESS-AKI goal is four (4) (0.25ml aliquots). If more than the minimum amount (0.175mL) of plasma were collected, but the goal amount (0.5mL) of plasma was not reached, one 0.150mL aliquot should be prepared for the Central Lab to evaluate sCr and Cystatin C and the remaining plasma should be prepared for the Bio repository. Q1050 should be answered 1 in this case.
- Q1060. Record if an extra aliquot was produced.
- Q1070. If there is an additional aliquot, estimate the amount of plasma saved and report to the nearest hundredth ml.
- Q1080. Record the date the aliquots were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1090. Record the time aliquots were frozen using a 24-hour clock. Aliquots should be stored in a --80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.

4.F.3.b Urine Specimen Processing

- Q1100. If there are no urine samples to be processed, complete the site specific worksheet and proceed to the Biological Sample Tracking module and enter all records.
- Q1110. Record the number of 1.0mL aliquots of urine produced. The ASSESS-AKI goal is 10 (1.0mL aliquots).

- Q1120. COMPLETE ONLY IF PARTICIPANT IS A DIAPER WEARER. Record if an extra aliquot was produced
- Q1130. Record the number of 10mL aliquots of urine produced. The ASSESS-AKI goal is 1 (10mL aliquots).
- Q1140. Record the date the aliquots were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1150. Record the time aliquots were frozen using a 24-hour clock. Aliquots should be stored in a --80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- If you need to process/spin the blood or urine samples a second time, include a comment in Q6000.
- If multiple collection attempts are made, complete the Pediatric Outpatient V12M Specimen Processing 2+ (P2_V12M_PROCESS_2) form(s).
- When the LAST collection attempt has been completed for the visit, enter all appropriate samples into the Biological Sample Tracking module.

4.F.4 P2_V12M_BLOOD_LOG

- At Visit 12M, affix each label from your barcode label sheet next to the appropriate sample and aliquot number displayed on the log for each sample collected.
- If multiple collection attempts are completed within the 48-hour period or within the outpatient visit window, multiple logs should be used.
- Complete one log for each collection date.
- If the DNA sample is collected at V24M, it will be entered into the BST as V12M and recorded on the V12M blood log.
- Use the logs when entering the blood samples into the BST.
- This log will be stored at the clinical center and should not be sent to the DCC.
- This log will be reviewed during ASSESS-AKI site visits.

4.F.5 P2_V12M_URINE_LOG

- At Visit 12M, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- If multiple collection attempts are completed within the 48-hour period or within the outpatient visit window, multiple logs should be used.
- Complete one log for each collection date.
- Use the logs when entering the urine samples into the BST.
- This log will be stored at the clinical center and should not be sent to the DCC.

- This log will be reviewed during ASSESS-AKI site visits.

4.F.6 P2_V12M_SAMPLE PRIORITY

- This form serves as a guide to the Research Coordinator in collecting and shipping the blood and urine samples in order of priority. Please collect and ship the samples following the priority order outlined on the checklist.
- This form is not entered during data entry and should not be sent to the DCC.

4.G Outpatient Visit Forms: PEDIATRICS

4.G.1 P2_OUTPT_COLLECT_BLD

- Complete the Visit Date as the current date the Pediatric Outpatient Specimen Collection: Blood (P2_OUTPT_COLLECT_BLD) form is completed.
- Q1000. This question is completed for home visits only to indicate if extra time will be allowed between collection and processing.
- Q1010. Record the date of the blood draw. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1020. Record the time blood specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1030. Record if the plasma sample was collected.
  - IF NO, reschedule another collection within 48 hours of this collection and complete the Pediatric Outpatient Specimen 2+ Collection: Blood (P2_OUTPT_COLLECT_BLD_2) form.
  - IF NO, and another collection cannot be completed within the 48-hour period, reschedule another within the visit window.
  - IF NO, and another collection cannot be scheduled within the 48-hour period and another outpatient visit cannot be completed within the visit window, stop completion of the form.
- Q1040. Record the method of blood collection ONLY IF BLOOD SAMPLE WAS COLLECTED.
- Q1050. Record if the EDTA purple top vacutainer was collected.
- IF DNA samples were not collected at V12M, prepare to attempt the DNA blood draw at the next visit.
- Complete the site specific worksheet.
- If another collection is successfully completed within 48 hours of the initial collection, complete the Outpatient Specimen 2+ Collection: Blood (P2_OUTPT_COLLECT_BLD_2) form.
  - The 2+ forms should only be entered into the database when the last collection attempt is completed within the 48-hour period.
  - The 2+ forms are entered into the database as single forms.
- If another collection is completed within the visit window, the forms completed at the rescheduled visit will be used for entry into the database and should be sent to the DCC.
  - The original outpatient (V24M, V36M, V48M, V60M, V72M, and V84M) forms can be stored at the site.

4.G.2 P2_OUTPT_COLLECT_UA

- Complete the Visit Date as the current date the Pediatric Outpatient Specimen Collection: Urine (P2_OUTPT_COLLECT_UA) form is completed.

- Q1000. This question is completed for home visits only to indicate if extra time will be allowed between collection and processing.
- Q1020. Record the date of the urine collection. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1030. Record the time urine specimen samples were collected using a 24-hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- Q1035. Record if the participant is wearing a diaper.
- NOTE: If a participant collects a urine sample at home and brings it to the visit, enter the date sample collected by the participant in Q1020, the time sample collected by the participant in Q1030, and answer Q1035 regarding the participant's diaper-wearing status. Q1040 should be left missing for samples collected at home by the participant.
- Q1040. Record the method used to collect the urine sample.
- Q1050. Was the urine sample collected?
  - IF NO, reschedule another collection within 48 hours of this collection and complete the Pediatric Outpatient Specimen 2+ Collection:Urine (P2_OUTPT_COLLECT_UA_2) form.
  - IF NO, and another collection cannot be completed within the 48-hour period, reschedule another outpatient visit within the visit window.
- Complete the site specific worksheet.
- If another collection is successfully completed within 48 hours of the initial collection, complete the Pediatric Outpatient Specimen 2+ Collection:Urine (P2_OUTPT_COLLECT_UA_2) form.
  - The 2+ forms should only be entered into the database when the last collection attempt is completed within the 48-hour period.
  - The 2+ forms are entered into the database as single forms.
- If another collection is completed within the visit window, the forms completed at the rescheduled visit will be used for entry into the database and should be sent to the DCC.
  - The original outpatient (V24M,V36M, V48M, V60M, V72M, and V84M) forms can be stored at the site.

4.G.3 P2_OUTPT_PROCESS

- Complete the Visit Date as the current date the Pediatric Outpatient Specimen Processing (P2_OUTPT_PROCESS) form is completed.
- Q995. Record and enter the sample collection date into the database. This is an additional field included on the Pediatric Outpatient Specimen 2+ Processing (P2_OUTPT_PROCESS_2) form.

4.G.3.a Blood Specimen Processing

- Q1000. If there are no blood samples to be processed, complete the site specific worksheet and proceed to Question 1070.

- Q1010. Record if there is a 0.5mL aliquot. If more than the minimum plasma was collected, but the goal amount was not reached, one 0.150ml should be prepared for the Central Lab to evaluate Scr and Cystatin C. Q1010 should be answered 1 in this case.
- Q1020. Record if there is a 0.25mL aliquot. If more than the minimum plasma was collected, but the goal amount was not reached, one aliquot should be prepared for the Bio Repository with the remaining amount after the 0.150ml aliquot is prepared for the Central Lab. Q1020 should be answered 1 in this case.
- Q1030. Record if an extra aliquot was produced.
- Q1040. If there is an additional aliquot, estimate the amount of plasma saved and report to the nearest hundredth ml.
- Q1050. Record the date the aliquots were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1060. Record the time aliquots were frozen using a 24-hour clock. Aliquots should be stored in a --80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.

4.G.3.b Urine Specimen Processing

- Q1070. If there are no urine samples to be processed, complete the site specific worksheet and proceed to the Biological Sample Tracking module and enter all records.
- Q1080. Record the number of 1.0mL aliquots of urine produced. The ASSESS-AKI goal is 10 (1.0mL aliquots).
- Q1090. Record the number of 10mL aliquots of urine produced. The ASSESS-AKI goal is 1 (10mL aliquots).
- Q1100. Record the date the aliquots were frozen. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.
- Q1110. Record the time aliquots were frozen using a 24-hour clock. Aliquots should be stored in a --80°C freezer. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15.
- If you need to process/spin the blood or urine samples a second time, include a comment in Q6000.
- If multiple collection attempts are made, complete the Pediatric Outpatient Specimen Processing 2+ (P2_OUTPT_PROCESS_2) form(s).
- When the LAST collection attempt has been completed for the visit, enter all appropriate samples into the Biological Sample Tracking module.

4.G.4 P2_VXXM_BLOOD_LOG

- At Outpatient Visits, affix each label from your barcode label sheet next to the appropriate sample and aliquot number displayed on the log for each sample collected.

- If multiple collection attempts are completed within the 48-hour period or within the outpatient visit window, multiple logs should be used.
- Complete one log for each collection date.
- If the DNA sample is collected, it will be entered into the BST as V12M and recorded on the V12M blood log.
- Use the logs when entering the blood samples into the BST.
- This log will be stored at the clinical center and should not be sent to the DCC.
- This log will be reviewed during ASSESS-AKI site visits.

4.G.5 P2_VXXM_URINE_LOG

- At Outpatient Visits, affix each label next to the appropriate sample and aliquot number displayed on the log. The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- If multiple collection attempts are completed within the 48-hour period or within the outpatient visit window, multiple logs should be used.
- Complete one log for each collection date.
- Use the logs when entering the urine samples into the BST.
- This log will be stored at the clinical center and should not be sent to the DCC.
- This log will be reviewed during ASSESS-AKI site visits.

4.G.6 P2_VXXM_SAMPLE PRIORITY

- This form serves as a guide to the Research Coordinator in collecting and shipping the blood and urine samples in order of priority. Please collect and ship the samples following the priority order outlined on the checklist.
- This form is not entered during data entry and should not be sent to the DCC.

4.H Storage

One 5-10mL cryovial containing packed cells from blood collected in an EDTA tube at V0 for DNA is to be stored at the site until the completion of the 12-month visit (or subsequent visits until a DNA sample collected in an ACD-A tube is obtained). If unable to obtain sample for cell line using the ACD-A tube at annual visits, ship the stored 5-10mL cryovial with packed cells from V0 to the Central Lab for DNA extraction. If the packed cells are not needed, the tube should be over labeled with TRIBE label.

For all other tubes:

- Immediately freeze all other tubes at –80°C after they have been scanned into the ASSESS-AKI Biological Sample Tracking system (BST).
- Store in the upright position until shipped.
- In exceptional cases, when the --80°C freezer is not available or broken, the samples can be stored at -20 for short-term (less than seven (7) days). Add comment to this effect on Pediatric Outpatient V3M Specimen Processing (P2_V3M_PROCESS), Pediatric Outpatient V12M Specimen Processing (P2_V12M_PROCESS), or Pediatric Outpatient Yearly Specimen Processing (P2_OUTPT _PROCESS) forms. Do NOT use a frost-free freezer.

4.I Instructions for Scanning the Biosamples into the Biological Sample Tracking (BST) Module

1. Log into the ASSESS website and select the Application link
2. Select Launch ASSESS AKI Application
3. Log onto the Biological Sample Tracking module
4. Select the Enter/Update/Search Sample Tracking
5. Enter your Participant ID and the Visit Number and select the Sample Type
6. Enter the Collection Date and select 'Execute Query/Insert Samples'
    - If multiple collection attempts were completed within the 48-hour period or within the visit window, there will be multiple blood/urine specimen logs.
    - If you have multiple collection logs, do not pre-populate the date for all records.
    - Scan each barcode from the logs, adding the collection date(s) as necessary.
7. When your barcodes have been scanned, review all of the data on the screen and verify that all the fields are correct.
    - If the default value does not match the volume in the scanned tube, the Sample Volume MUST be changed.
    - Refer to the ASSESS General MOP, Section 10.B.5 for detailed instructions on updating the samples.
8. When the information matches the log and is correct for all fields, select Insert Samples
9. Next Exit out of the 'Enter/Update/Search' Sample Tracking and go to the 'Build a Shipment' Link
10. Scan or enter your barcode IDs from the P2_V3M_BLOOD_LOG/P2_V12M_BLOOD_LOG/P2_VXXM_BLOOD_LOG and P2_V3M_URINE_LOG/P2_V12M_URINE_LOG/P2_VXXM_URINE_LOG for the biosamples, again you should see these records appear below with the information
    - Citrate tube for DNA collection should be entered into the BST as DNA tube.
11. Once the records appear on the screen, select the 'Exit Build Shipment' link
12. Next go into the View Shipments – Mark as Shipped/Print Logs
13. You should see your build in progress, select the Ship button
14. Enter a Date Shipment Sent, the tracking number, comments and select Save
15. Select the Print Log link and save the file to your desktop and/or print and scan a copy. Also select the Create Export File link. Save this file to your desktop.
16. Email the appropriate lab and copy the ASSESS_LAB alias once your shipment is ready and will be sent out that day with the appropriate lab shipping (instructions found below in Section 5).

5 NIDDK REPOSITORY (PRECISION FOR MEDICINE)

5.A Overview

On March 01, 2018, The NIDDK Repository transitioned the NIDDK Biorepository from Fisher and Rutgers to Precision for Medicine (Precision). The transition period, including the physical relocation of all freezers, liquid nitrogen tanks, and other repository materials was completed by March 30, 2018 and normal repository operation resumed on April 09, 2018 at Precision.

5.B Contact Information

Precision for Medicine
8425 Precision Way, Suite M
Frederick, MD 21701

Eduard Chani PhD
Senior Project Manager
Email: eduard.chani@precisionformedicine.com
240-415-6052 office
301-318-8218 mobile
301 668 3416 fax

Requests for supplies (cryovials, freezer storage boxes, labels, etc.) should be sent to Precision for Medicine at niddk.mailbox@precisionformedicine.com; CC Eduard.chani@precisionformedicine.com. All requests for supplies should be sent to Precision. When possible, please submit requests at least seven days in advance, please include your site number and that this is for ASSESS_AKI in your request.

5.C Schedule of Shipment

Shipments are to be sent on Tuesdays and Wednesdays only. After November 30, 2017, only the University of Washington is shipping samples.

	Schedule of Shipment to NIDDK Biorepository
UW	Every other week

6 NIDDK REPOSITORY (FISHER AND RUTGERS) AND CENTRAL LAB

6.A Overview

The NIDDK Repository (Fisher) will receive aliquots of urine and blood during the inpatient and outpatient phases from all sites. On or before November 30, 2017, Cincinnati, Montreal, London, New Haven, Vanderbilt, and Kaiser ended their sample collection and participant contact. The University of Washington continues collection and participant contact.

On March 01, 2018, The NIDDK Repository transitioned the NIDDK Biorepository from Fisher and Rutgers to Precision for Medicine (Precision).

For adult participants, the Central Lab will receive one 1.0mL aliquot of urine and one 1.0mL aliquot of serum for the core measurements during the outpatient phase. For pediatric participants, the Central Lab will receive one 1.0mL aliquot of urine and one 0.5mL aliquot of plasma for the core measurements during the outpatient phase.

The NIDDK Repository (Rutgers) will receive blood collected at V12M from only the pediatric sites.

6.B Those who ship samples to the NIDDK Biorepository (Fisher and Rutgers) and/or the Central Lab must have IATA/DOT infectious substances certification. Please contact your institutional safety office for more information. Please forward copies of the certification to ASSESS_LAB.

6.C NIDDK Repository (Fisher)

6.C.1 Contact Information

6.C.2 Shipping Inpatient Samples

A shipper will hold~243 x 2ml vials.

The Repository will provide shipping kits to the sites with the following components:

- Insulated shipper
- 3 biohazard bags
- 3 absorbent sheets
- 3 envelopes
- 3 specimen boxes with 9 x 9 cell dividers
- Inner cardboard box
- Preprinted FedEx air bill
- Repository address label
- Class 9 miscellaneous dangerous goods label
- UN 3373 Category B label

- Cardboard address piece

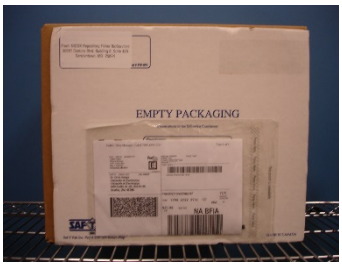
Follow the instructions for packaging samples, assembling the kit and shipping samples to the Repository. Only for the University of Washington, its HMC mailroom requests that FEDEX mailing labels be placed on top of the shipping box.

6.C.3 Schedule of Shipment

Shipments are to be sent on Tuesdays and Wednesdays only.

	Schedule of Shipment to NIDDK Biorepository
Cincinnati	Monthly
Montreal	Monthly
London	Every two weeks
New Haven	Every 2 months
Vanderbilt	Every two weeks
Kaiser	Every two months
UW	Every other week

6.C.4 Assembling the STP320 Repository Shipper



1. Upon receipt of the empty shipping kit from the NIDDK Biosample Repository, remove the "EMPTY PACKAGING" cardboard piece from the outer box.
2. Place up to 81 x 2ml cryovials in each specimen box. When packing vials, place them in the specimen boxes left to right, top to bottom. Group vials together by patient and visit.
3. Place each specimen box and an absorbent sheet inside a plastic biohazard bag. Seal the bag.
4. Place each plastic biohazard bag inside a white Tyvek envelope. Seal the envelope.
5. Place the Tyvek envelopes in the cardboard inner box. If only two specimen boxes are being shipped, fill the rest of the space inside the cardboard inner box with packing material (e.g., bubble wrap) or an empty specimen box to prevent movement during shipment. Close and tape the inner cardboard box and set it in the middle of the cooler.

6. Completely fill the space between the inner cardboard box and the inner walls of the cooler with dry ice pellets.
7. Place the lid on the cooler. Place the "EMPTY PACKAGING" cover and shipping log on top of the cooler lid.
8. Close and tape the outer cardboard box.

9. Place a checkmark in the block on the outer cardboard box next to "BIOLOGICAL SUBSTANCE, CATEGORY B". Do not cover this marking with labels.
10. Affix a label with your name and return address to the side of the box in the "Shipper:" block.
11. Affix the repository address label to the side of the box in the "Consignee:" block.
12. Affix the dry ice label below the repository address label. Enter the weight of dry ice on the label in kilograms.
13. Affix the "UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B" label to the right of the dry ice label.

14. Note to the Canadian sites: Add the following statement to your commercial invoice form "These samples are for research use only. They have no commercial value and are supplied free of charge."
15. Verify that the box contains the pre-printed FedEx Waybill, with Ice listed on the bottom right side of the waybill and that label is address to: Eduard Chani at Precision for Medicine- 8425 Precision Way, Suite M Frederick, MD 21701.

16. If this label is not available, please contact: niddk.mailbox@precisionformedicine.com and request an electronic waybill.
17.
18. Call Federal Express at 1-800-GO-FEDEX (1-800-463-3339). Give them the account number on the preprinted FedEx air bill (in Section 7, Payment) and your pickup address. FedEx will dispatch a courier to pick up the package. Please schedule shipments Tuesday through Wednesday. **Do not ship samples on, Thursdays, and Fridays to ensure sample integrity due to courier delays.**

19. Send a shipment notification to the repository via email with the data export file to **niddk.mailbox@precisionformedicine.com** and copy the ASSESS_LAB on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number in the notification and the estimated time of arrival.

20. Contact the NIDDK Biosample Repository via email or call Bernadette Owen (240-206-4120) or Eduard Chani (240-415-6052) regarding questions about packaging and shipping.

6.D Central Laboratory

6.D.1 Contact Information

Advanced Research and Diagnostic Laboratory
ASSESS Study
1200 Washington Ave S, Suite 175
Minneapolis, MN 55415

6.D.2 Shipping Samples to Central Laboratory

The Central Laboratory will provide the following shipping supplies:

- Frozen Sample Shipment
  - Insulated Shipper
  - Specimen Boxes
  - Plastic Bags
  - Absorbent Sheets
  - Preprinted FedEx airbill
  - Dry ice label
  - Exempt Human Specimen label
  - In addition to the supplies listed above, you will need:
  - Five pounds dry ice (2.25 kg)

6.D.3 Schedule of Shipment

Ship frozen samples to the central laboratory on Tuesdays and Wednesdays only.

	Schedule of Shipment to Central Lab
Cincinnati	1st Tuesday of the Month
Montreal	2nd Week of the Month
London	Every two weeks
New Haven	4th Tuesday of the Month
Vanderbilt	Every two weeks
Kaiser	1st Wednesday of the Month
UW	Every week

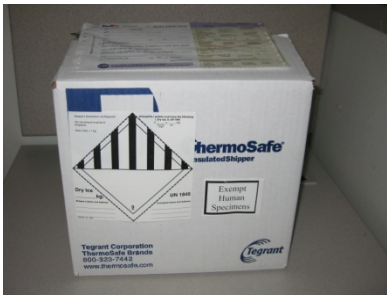
6.D.4 Assembling Frozen Sample Shipments to the Central Laboratory

1. Place up to 80 x 2mL cryovials in each specimen box. When packing vials, place them in the specimen boxes left to right, top to bottom. Group vials together by patient and visit.
2. Place each specimen box and an absorbent sheet inside a plastic bag. Seal the bag.
3. Place packed cell aliquots in separate plastic bag with an absorbent sheet and seal the bag.

4. Place a layer of dry ice pellets on the bottom of Styrofoam shipping box. Place plastic bag with box of aliquots on top of dry ice layer. Place bag of packed cell aliquots beside the specimen box, on top of dry ice layer. Place additional dry ice pellets on top of specimens. Use at least five pounds (2.25 kg) of dry ice in each shipping box.
5. Place lid on the Styrofoam box. Place the shipping logs on top of Styrofoam cover.

6. Close and tape the outer cardboard box.
7. Affix a dry ice label on the side of the shipping box. Enter the weight of dry ice on the label.
8. Affix the "Exempt Human Specimens" label to the side of the shipping box, near the dry ice label.
9. Note to Canadian sites: Add the following statement to your commercial invoice form "These samples are for research use only. They have no commercial value and are supplied free of charge".

10. Use the pre-printed FedEx airbill to ship specimens to the Central Laboratory. (University of Minnesota Medical Center, Fairview)
    a. Section 1: Fill in the date, your name, phone number and return address.
    b. Section 6: Special Handling: Check "Yes, Shipper's Declaration not required". Check the "Dry Ice" box; enter "1" and the weight of dry ice.
    c. Section 7: Enter "1" under total packages and the total weight of the package.
    d. Follow the peel-and-stick instructions on the back of the airbill. As shown, affix the airbill to the top of the box.



11. Call Federal Express at 1-800-GO-FEDEX (1-800-463-3399). Give them the account number on the preprinted FedEx airbill (in Section 7, Payment) and your pickup address. FedEx will dispatch a courier to pick up the package. Please schedule shipments Tuesday through Wednesday. Do not ship samples on Mondays, Thursdays, and Fridays.

12. Send a shipment notification to the central lab via email with the export data file, and copy the ASSESS_LAB on the day the package is picked up by FedEx. You will receive an email notification from the Central Laboratory within two (2) business days of receipt of the samples.
13. Contact the Central Laboratory regarding questions about packaging and shipping.

6.E *Holiday Closure Table for the NIDDK Biorepository (Precision for Medicine)and Central Laboratory*

Holiday	NIDDK Biorepository (Precision)	Central Lab
New Years Day		Closed
Martin Luther King, Jr. Day		Normal Business Hours
Washington's Birthday		Normal Business Hours
Memorial Day		Closed
Independence Day		Closed
Labor Day		Closed
Columbus Day		Normal Business Hours
Veterans Day		Normal Business Hours
Thanksgiving Day		Closed
Day after Thanksgiving Day		Normal Business Hours
Christmas Eve		Normal Business Hours
Christmas Day		Closed

BIOREPOSITORY (Precision): DO NOT SHIP TWO DAYS BEFORE A HOLIDAY. For example, if a holiday falls on a Friday, do not ship on the prior Wednesday or Thursday.

CENTRAL LAB: WILL SEND EMAIL REMINDERS PRIOR TO THE HOLIDAYS THAT THEY ARE CLOSED IF SPECIAL SHIPPING SCHEDULES SHOULD BE FOLLOWED.

6.F *Holiday Closure Table for the NIDDK Biorepository (Fisher) and NIDDK Biorepository (Rutgers)*

Holiday	NIDDK Biorepository (Fisher)	Biorepository (Rutgers)
New Years Day	Closed	Closed
Martin Luther King, Jr. Day	Closed	Normal Business Hours
Washington's Birthday	Closed	Normal Business Hours
Memorial Day	Closed	Closed
Independence Day	Closed	Closed
Labor Day	Closed	Closed
Columbus Day	Closed	Normal Business Hours
Veterans Day	Normal Business Hours	Normal Business Hours
Thanksgiving Day	Closed	Closed
Day after Thanksgiving Day	Closed	Normal Business Hours
Christmas Eve	Closed	Normal Business Hours
Christmas Day	Closed	Closed

NIDDK BIOREPOSITORY (Fisher, Rutgers): DO NOT SHIP TWO DAYS BEFORE A HOLIDAY. For example, if a holiday falls on a Friday, do not ship on the prior Wednesday or Thursday.

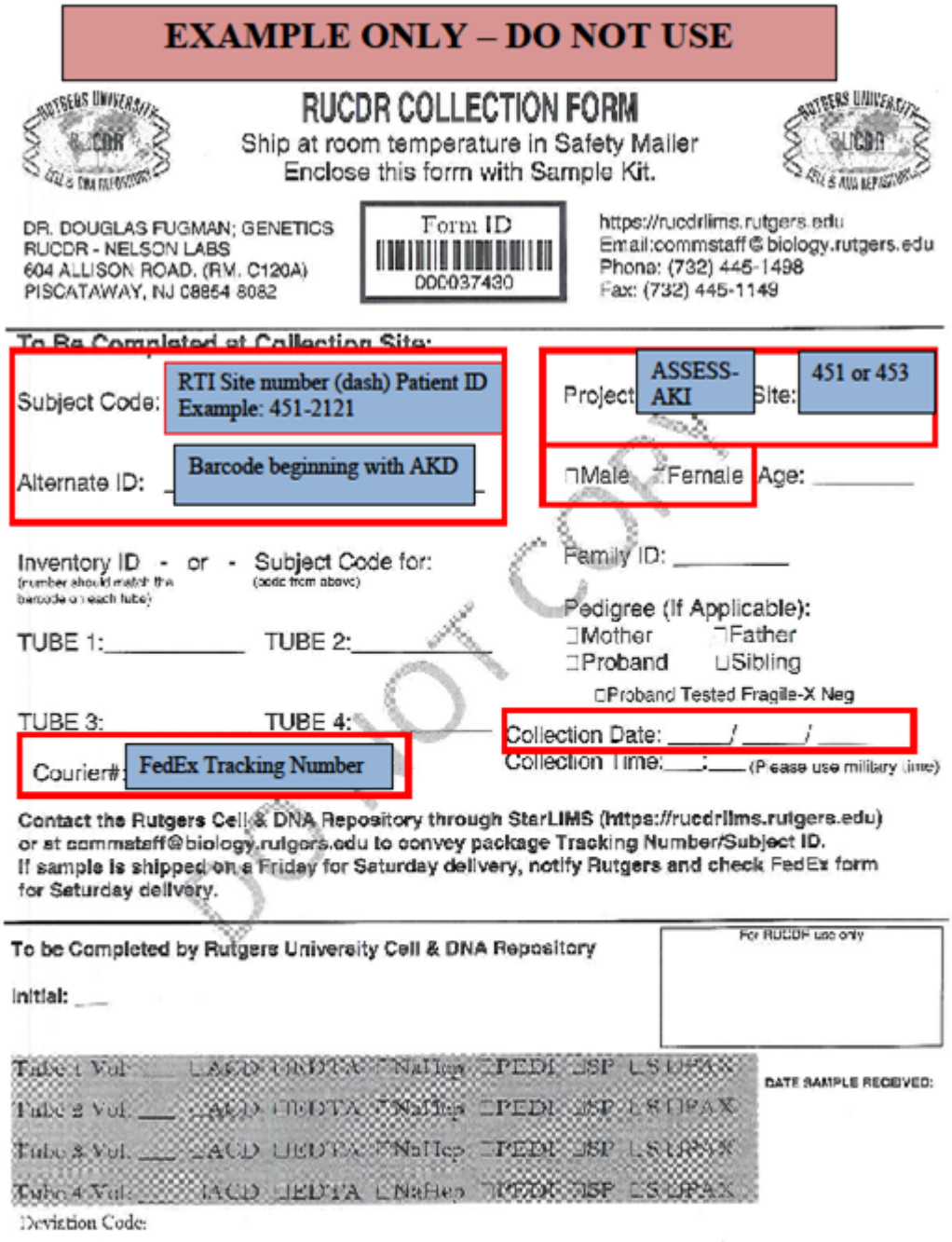
6.G NIDDK Repository (Rutgers) – Pediatric Sites Only

6.G.1 Contact Information

Genetics
RUCDR – NELSON LABS
604 Allison Road, Rm. C120A
Piscataway NJ 08864-8082

6.G.2 Pediatric DNA Cell-line Immortalization

- Complete and attach ID labels to the tubes making sure the label does not cover the barcode on the tube. DO NOT write the patient's name or any other personal identification information (e.g. SS#, DOB) on the tubes.
- Collect blood specimen in the yellow top (ACD) tube provided. Be sure to invert the tube gently 8 to 10 times to mix blood with additives and keep the tube at room temperature.
- On the RUCDR Collection Form fill in the following fields:
    a. Subject Code – the patient's unique ID number (RTI-participant ID, example: 451-2121)
    b. Alternate ID – barcodes from each tube
    c. Inventory ID – barcode on the tube when it was received
    d. Collection Date
    e. Project – ASSESS-AKI
    f. Site – NIDDK site number (Cincinnati enter 451, Montreal enter 453)
    g. Sex/Age - complete gender/sex, age is optional
    h. Family ID and Pedigree – if applicable
    i. Courier # - tracking number for package
- Double check that the ID information on tube matches that on the RUCDR Collection Form.



EXAMPLE ONLY – DO NOT USE

RUCDR COLLECTION FORM

Ship at room temperature in Safety Mailer
Enclose this form with Sample Kit.

DR. DOUGLAS FUGMAN; GENETICS
RUCDR - NELSON LABS
604 ALLISON ROAD, (RM. C120A)
PISCATAWAY, NJ 08854 8082

Form ID
DDD037430

https://rucdrlims.rutgers.edu
Email:commstaff@biology.rutgers.edu
Phone: (732) 445-1498
Fax: (732) 445-1149

To Be Completed at Collection Site:

Subject Code: RTI Site number (dash) Patient ID Example: 451-2121

Alternate ID: Barcode beginning with AKD

Project: ASSESS-AKI Site: 451 or 453

☐Male ☐Female Age: _____

Inventory ID - or - Subject Code for:
(number should match the barcode on each tube) (code from above)

TUBE 1:_____ TUBE 2:_____

TUBE 3: TUBE 4:

Courier#: FedEx Tracking Number

Family ID: _____

Pedigree (If Applicable):
☐Mother ☐Father
☐Proband ☐Sibling
☐Proband Tested Fragile-X Neg

Collection Date: ____/____/____
Collection Time: ___:___ (Please use military time)

Contact the Rutgers Cell & DNA Repository through StarLIMS (https://rucdrlims.rutgers.edu) or at commstaff@biology.rutgers.edu to convey package Tracking Number/Subject ID. If sample is shipped on a Friday for Saturday delivery, notify Rutgers and check FedEx form for Saturday delivery.

To be Completed by Rutgers University Cell & DNA Repository

Initial: ___

For RUCDR use only

Tube 1 Vol. ___ ☐ACD ☐EDTA ☐NaHep ☐PEDI ☐SP ☐SUPAX

Tube 2 Vol. ___ ☐ACD ☐EDTA ☐NaHep ☐PEDI ☐SP ☐SUPAX

Tube 3 Vol. ___ ☐ACD ☐EDTA ☐NaHep ☐PEDI ☐SP ☐SUPAX

Tube 4 Vol. ___ ☐ACD ☐EDTA ☐NaHep ☐PEDI ☐SP ☐SUPAX

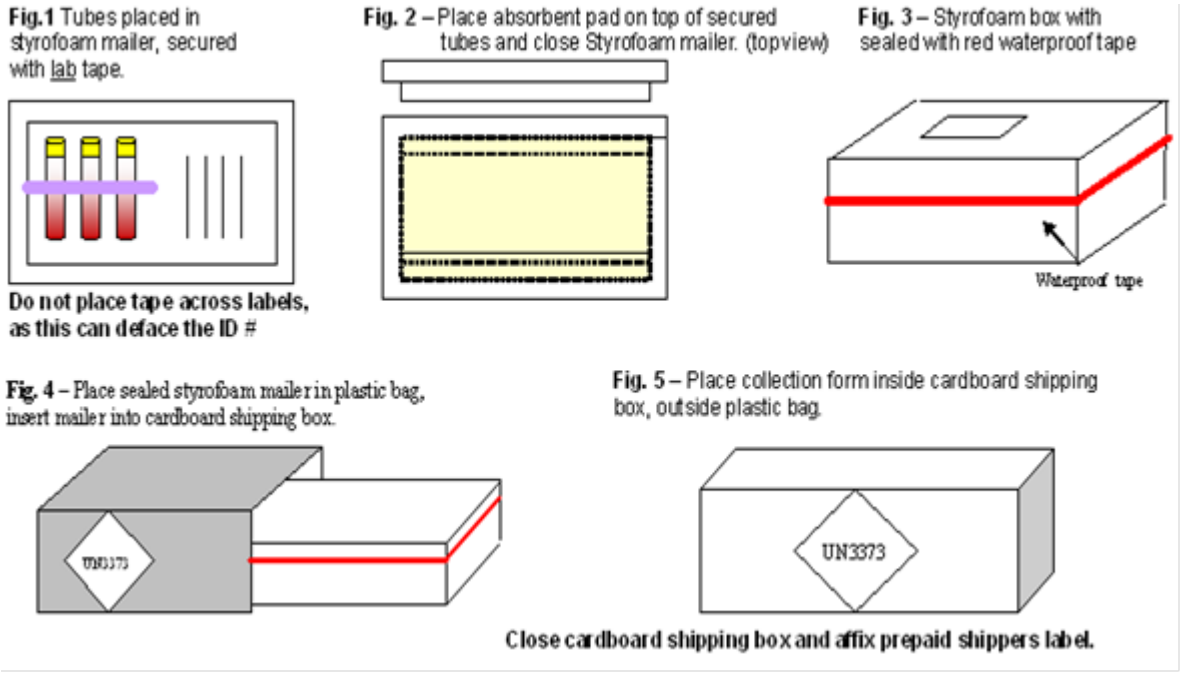
DATE SAMPLE RECEIVED:

Deviation Code:

- Please notify Rutgers University Cell and DNA Repository that you are shipping the sample by logging into STARLIMS at the following website http://www.rucdr.org/lims.htm.
- Call Federal Express (1-800-GO-FEDEX) to schedule a pick-up. Be sure to give FedEx the zip code of the pickup address, not that of the destination. Do not put mailer in a FedEx drop box.
- If the sample cannot be shipped the same day, keep the specimen at room temperature and immediately ship the next day. Do not freeze the specimen. Avoid placing the specimen in a warm location above room temperature.

6.G.2.a Instructions for Cincinnati Site

Pack the tubes in the kit using the directions below



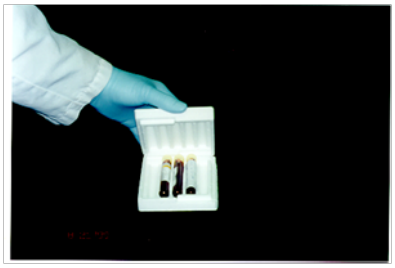
Send a shipment notification to the Rutgers lab via:

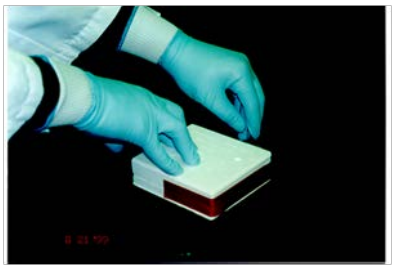
Commstaff@dls.rutgers.edu on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number in the notification and cc the following address assess_lab@phs.psu.edu. Include the export file and an estimated time of arrival for your samples to the Rutgers lab.

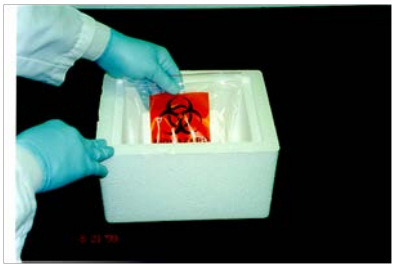
A representative at the Rutgers lab will then email you back as well as cc the assess_lab@phs.psu.edu address with receipt of the tube.

6.G.2.b Instructions for Montreal Site

1. Place tubes into the small Styrofoam insert.
2. Tape the Styrofoam insert closed.
3. Place the Styrofoam insert into the Biohazard, seal the bag, and place in the large Styrofoam mailer. INCLUDE A COPY OF THE RUCDR COLLECTION FORM IN THE LARGE STYROFOAM MAILER.
4. Tape the large Styrofoam mailer closed.
5. Slide the Styrofoam mailer into the cardboard carton and seal with packing tape. Place the Federal Express International Shipping form and any other Necessary documents (i.e. Declaration Statement, Customs Invoice) on the outside of the carton.
6. Note to Canadian site: Add the following statement to your commercial invoice form "These samples are for research use only. They have no commercial value and are supplied free of charge."







Send a shipment notification to the Rutgers lab via Commstaff@dls.rutgers.edu on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number in the notification and cc the following address assess_lab@phs.psu.edu. Include the export file and an estimated time of arrival for your samples to the Rutgers lab.

A representative at the Rutgers lab will then email you back as well as cc the ASSESS_LAB with receipt of the tube.

6.G.3 STARLIMS Sample Submission to Rutgers

The RUCDR STARLIMS Sample Submission video will show you how to submit samples to the RUCDR. You can access the video by going to http://rucdr.org. Click on the LIMS link on the top navigation menu, then the TRAINING VIDEOS link on the left navigation menu. Then, click on RUCDR STARLIMS Sample Submission.

If you do not have access to the RUCDR STARLIMS Sample Submission video, then follow the following instructions:

1. Go to LOGIN OPTIONS on the right side of the screen. Choose the SAMPLE SUBMISSION option.
2. This will automatically enter you as submitter.
3. Choose the PROJECT, then the SITE.
4. Choose the courier, which typically is FedEx. Enter the tracking number, then in the NOTES field, enter in any special instructions.
5. Note that all items with an asterisk are required.
6. To manually add samples, click on MANUALLY ADD SAMPLES TO THE LIST. The screen entitled SAMPLE INFORMATION will pop up.
7. Scan the barcode on the phlebotomy form that was inside of your kit. If you do not have a scanner, enter the barcode number into the FORM NUMBER field and press enter.
8. Enter the SUBJECT ID, according to the naming convention for your study.
9. Enter the ALTERNATE ID, PEDIGREE, SEX, and AGE.
10. By default, the day and time are selected. In the event the sample was collected at an earlier date, that information can be entered. However, later dates are not accepted.
11. All entries with an asterisk are required.
12. Next, the information for each tube needs to be entered into the SAMPLE INFORMATION pop up. There are two options, depending on whether or not the tubes in your kits have a preprinted barcode.
13. If you DO have a preprinted barcode on your tube, choose the sample source, which will in most cases is whole blood (indicated by WB) or saliva, cell lines, DNA, or blood spot cards.
14. Click on the INVENTORY ID window and either scan the barcode on the tube or enter it manually.
15. The SUBJECT ID will automatically populate.
16. Click on ADD.
17. If this is a redraw of a previously collected subject, then check the box for a redraw. Check your data, and submit your request.
18. If you DO NOT have a preprinted barcode on your tube, choose the sample source, which is most likely whole blood.
19. The SUBJECT ID is automatically populated. Click in the SUBJECTID field.
20. Then, in order to select the container type, click on the pull-down menu.

21. Choose the CONTAINER TYPE.
22. Click on ADD.
23. Whether or not you have a preprinted barcode on your tube, every tube submitted for processing needs to be entered into the system.
24. Once you have completed entering and adding the information for each tube in the SAMPLES section, click on SAVE.
25. Your sample list will appear in the bottom section of the SAMPLE SUBMISSION page.
26. Choose the appropriate answer if the subject was a redraw.
27. Review your information and click on SUBMIT. A number will be assigned to each of your requests.
28. Click on YES.
29. From the customer dashboard, you can track your sample submission, as well as requests for supplies and biomaterials. You will receive email notification after the arrival and accessioning of your samples at the RUCDR.

Videos for requesting supplies and requesting biomaterials are also available. If you need further assistance, please contact the RUCDR STARLIMS helpdesk by phone at 732.445.4429 or email at starlimshelp@biology.rutgers.edu.

6.G.4 STARLIMS Request for Supplies

The RUCDR STARLIMS Request for Supplies video will show you how to order collection kits, forms, and additional supplies from the RUCDR. You can access the video by going to http://rucdr.org. Click on the LIMS link on the top navigation menu, then the TRAINING VIDEOS link on the left navigation menu. Then, click on RUCDR STARLIMS Request for Supplies.

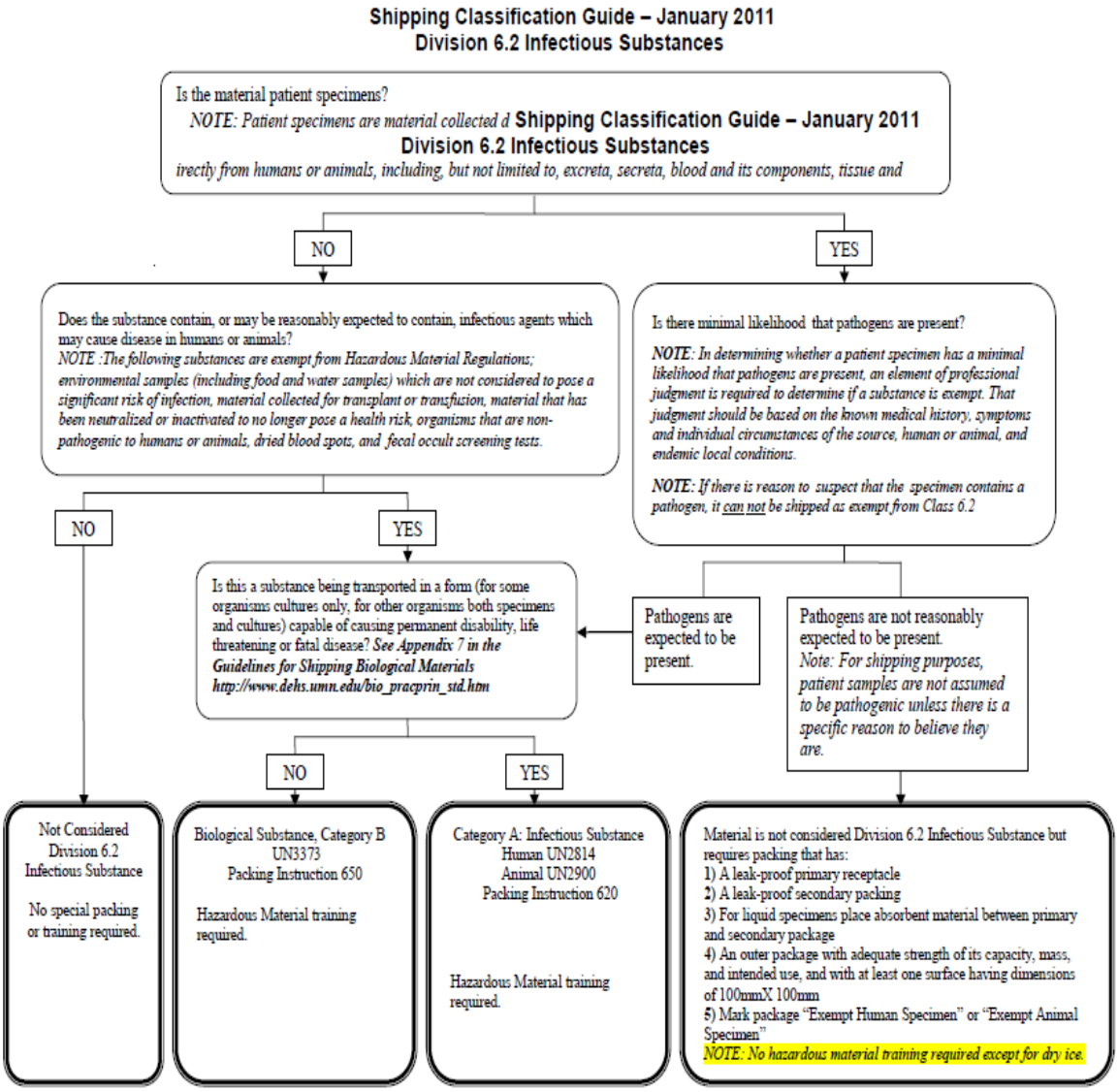
If you do not have access to the RUCDR STARLIMS Request for Supplies video, then follow the following instructions:

1. Under the INVENTORY MANAGEMENT OPTIONS, click on REQUEST FOR SUPPLIES.
2. Enter the PROJECT, SITE, and CONTACT NAME.
3. Your CONTACT EMAIL, PHONE and SHIPPING ADDRESS will automatically populate if registered into the system.
4. In the event there is no email or contact phone number associated with your account, they do need to be filled in for your submission to be completed. Also, if you would like to change the address that these supplies are being shipped to, click on EDIT ADDRESS. Be advised that this change will not become permanent but will only apply to this particular request.
5. If there are any special instructions, enter them in the LETTER/INFORMATION section.
6. In the MATERIALS section, enter the QUANTITY REQUESTED for each material.
7. If you need ten complete mailers and two yellow top tubes, for example, enter in the numbers “10” and “2” in the corresponding rows under QUANTITY REQUESTED.
8. If you do not see the supplies that you need, please contact the STARLIMS Help Desk at the RUCDR.

9. Review your information and click on SUBMIT. A number will be assigned to each of your requests.
10. From the customer dashboard, you can track your supply request, as well as sample preregistration and requests for biomaterials. You will receive email notification after your supplies are sent from the RUCDR.

Videos for sample preregistration and request for biomaterials are also available. If you need further assistance, please contact the RUCDR STARLIMS helpdesk by phone at 732.445.4429 or email at starlimshelp@biology.rutgers.edu.

6.H Shipping Classification Guide



6.I Biomarker Partner Laboratories

Lab doing analysis	Contact Person	Address of Lab
Keck Foundation Biotechnology Resource Lab		
Univ of Vermont, Dept of Pathology		
Univ of Minn Advanced Research and Diagnostic Lab		

7 BIOSPECIMEN PROCESSING FOR THE SWAN STUDY

7.A Overview

- Blood and urine collection and processing is the same as it is for the ASSESS-AKI samples. Refer to Section 2 for biospecimen collection and processing for adults and Section 4 for biospecimen collection and processing for the pediatric population.
- If only the minimum of serum/plasma and/or urine is collected, do NOT include this participant in the SWAN study. Notify the DCC by email within one business day.
- For the adult sites, one serum cryovial and one urine cryovial intended for the NIDDK Biorepository will be relabeled for the Central Lab for five percent of the samples. Kaiser, Vanderbilt, and University of Washington will send 20 serum and 20 urine samples as duplicates per site, Yale New Haven and Yale London Ontario will send eight (8) serum and eight (8) urine samples per site.
- For the pediatric sites, one plasma cryovial and one urine cryovial intended for the NIDDK Biorepository will be relabeled for the Central Lab. Cincinnati will send four (4) plasma and four (4) urine samples as duplicates and Montreal will send two (2) plasma and two (2) urine samples.
- The SWAN study will be conducted at V3M, V12M, V24M, and V36M. The SWAN cryovials will be shipped with the regular ASSESS-AKI shipment.

7.B Assignment of Participant IDs

- Each SWAN Participant ID will include the Protocol number – Site number-SWAN ID
- We will use the following numbers as Participant IDs:
  - 0001 - 0200 for V3M samples,
  - 0201- 0400 for V12M samples,
  - 0401- 0600 for V24M samples, and
  - 0601 – 0800 for V36M samples.
- Sites will send a file via email on the 22nd (or next business day) of each month to the DCC using ASSESS_LAB alias. This file will be a list of current V0 participants who are scheduled for V3M for the following month. For example, the sites will email to the DCC on March 22nd the V0 participants who are scheduled to come for their V3M in the month of April. If the schedule changes or a participant withdraws, the site will notify the DCC within one business day.
- The DCC will select the participants from the list and assign the SWAN Participant IDs. The DCC will return the list with the SWAN Participant IDs and randomization order to the site on the 30th/31st of each month.
- This process will be repeated for participants scheduled for V12M, V24M, and V36M.

7.C Barcode Labels

- The barcode labels will be provided by the DCC. If additional barcode labels are necessary, allow a minimum five-work-day window for the DCC to generate and ship labels to the sites. SWAN barcodes will include the prefix:
  - AKX for plasma
  - AKY for serum
  - AKZ for urine
- One duplicate label will be printed for each participant along with a SWAN Participant Assignment Log.

7.D Labeling the Cryovials

1. Peel off one urine label with the prefix AKZ for the Central Lab and affix to a 2mL cryovial to perfectly cover the urine label with the prefix AKU for the NIDDK Biorepository. Make sure that the barcode is NOT under the cap. Affix the clear adhesive label while overlapping the ends of the clear adhesive label. Make sure that the label does not overlap on top of the barcode.

2. ADULT SITES: Peel off one serum label with the prefix AKY for the Central Lab and affix to a 2mL cryovial to perfectly cover the serum label with the prefix AKS for the NIDDK Biorepository. Make sure that the barcode is NOT under the cap. Affix the clear adhesive label while overlapping the ends of the clear adhesive label. Make sure that the label does not overlap on top of the barcode.

3. PEDIATRIC SITES: Peel off one plasma label with the prefix AKX for the Central Lab and affix to a 2mL cryovial to perfectly cover the plasma label with the prefix AKP for the NIDDK Biorepository. Make sure that the barcode is NOT under the cap. Affix the clear adhesive label while overlapping the ends of the clear adhesive label. Make sure that the label does not overlap on top of the barcode.

7.D.1 Collection Logs for Blood and Urine Aliquots

- The DCC will create a log, "SWAN Participant Assignment Log – Visit Number," where the columns are Participant ID, ASSESS Participant ID, Serum/Plasma label, and Urine label.
  - The sites will email these logs to the DCC by the 7th of every subsequent month so the DCC may verify the assignment of the SWAN IDs from the previous month.
- This log will link the SWAN ID to the ASSESS Participant ID for analysis and is only available to the individual site and the DCC
- Affix the duplicate serum/plasma and urine labels to the appropriate place on the SWAN Participant Assignment Log.
- The original copy of the log(s) will be stored at the clinical center.
- The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- On the ASSESS-AKI blood and urine logs make a note next to the record for the sample used for the SWAN study to indicate that it was sent for the SWAN study.

7.D.2 Instructions for Completing the Excel Spreadsheet

- Scan each barcode from the SWAN PARTICIPANT ASSIGNMENT LOG into the Excel spreadsheet. Yale Cincinnati will type the barcode rather than scan the barcode, due to its barcode scanner being unable to read the barcode.
- Volume, unit of measurement (UOM), and visit number are pre-populated.
- Type the Participant ID, specimen type, date of collection, date frozen, and shipment ID. There is a column for comments,
- When your barcodes have been entered and the information matches the log and is correct for all fields, print this file, and save it to your desktop.
- Add the Excel spreadsheet to your shipment to the Central Lab once your regular ASSESS-AKI shipment is ready.

7.E Instructions for Updating the BST for ASSESS

- Site removes the one serum/plasma and one urine sample with BIO (Biorepository) as the Destination Lab from the BST and selects "Other" as the reason for the exclusion. This is necessary to account for the collection and processing form checks.
- If you have not already done so make a note next to the record for the sample used for the SWAN study on the ASSESS-AKI blood and urine logs to indicate that it was sent for the SWAN study.

7.F Instructions for SWAN Shipment to the Central Laboratory

7.F.1 Shipping Samples to Central Laboratory

- Ship frozen samples to the central laboratory weekly.
- The Central Laboratory will provide the following shipping supplies:
- Frozen Sample Shipment
  - Insulated Shipper
  - Specimen Boxes
  - Plastic Bags
  - Absorbent Sheets
  - Preprinted FedEx airbill
  - Dry ice label
  - Exempt Human Specimen label
  - In addition to the supplies listed above, you will need:
  - Five pounds dry ice (2.25 kg)

7.F.2 Assembling Frozen Sample Shipments to the Central Laboratory

1. Place the SWAN 2mL cryovials into the ASSESS specimen box. When packing vials, place them in the specimen boxes left to right, top to bottom. Group vials together by patient and visit.
2. Place each specimen box and an absorbent sheet inside a plastic bag. Seal the bag.
3. Place packed cell aliquots in separate plastic bag with an absorbent sheet and seal the bag.

4. Place a layer of dry ice pellets on the bottom of Styrofoam shipping box. Place plastic bag with box of aliquots on top of dry ice layer. Place bag of packed cell aliquots beside the specimen box, on top of dry ice layer. Place additional dry ice pellets on top of specimens. Use at least five pounds (2.25 kg) of dry ice in each shipping box.
5. Place lid on the Styrofoam box. Place the ASSESS shipping logs and the SWAN Excel spreadsheet on top of Styrofoam cover.

6. Close and tape the outer cardboard box.
7. Affix a dry ice label on the side of the shipping box. Enter the weight of dry ice on the label.
8. Affix the "Exempt Human Specimens" label to the side of the shipping box, near the dry ice label.
9. Note to Canadian sites: Add the following statement to your commercial invoice form "These samples are for research use only. They have no commercial value and are supplied free of charge".

10. Use the pre-printed FedEx airbill to ship specimens to the Central Laboratory. (University of Minnesota Medical Center, Fairview)
    a. Section 1: Fill in the date, your name, phone number and return address.
    b. Section 6: Special Handling: Check "Yes, Shipper's Declaration not required". Check the "Dry Ice" box; enter "1" and the weight of dry ice.
    c. Section 7: Enter "1" under total packages and the total weight of the package.
    d. Follow the peel-and-stick instructions on the back of the airbill. As shown, affix the airbill to the top of the box.

11. Call Federal Express at 1-800-GO-FEDEX (1-800-463-3399). Give them the account number on the preprinted FedEx airbill (in section 7, Payment) and your pickup address. FedEx will dispatch a courier to pick up the package. Please schedule shipments Tuesday through Wednesday. Do not ship samples on Mondays, Thursdays, and Fridays.

12. Send a shipment notification to the Central Lab via email with the ASSESS export data file and SWAN Excel spreadsheet and copy the ASSESS_LAB on the day the package is picked up by FedEx. You will receive an email notification from the Central Laboratory within 2 business days of receipt of the samples.
13. Contact the Central Laboratory regarding questions about packaging and shipping.

8 BIOSPECIMEN PROCESSING FOR THE CLANS STUDY

8.A Overview

- Blood and urine collection and processing is the same as it is for the ASSESS-AKI samples. Refer to Section 2 for biospecimen collection. Cincinnati and Montreal, the pediatric sites, will not participate in CLANS.
- For the adult sites, one serum cryovial and one urine cryovial intended for the NIDDK Biorepository will be relabeled for the Central Lab for five percent of the samples. Vanderbilt will send 15 serum and 15 urine samples as duplicates per site; University of Washington will send 10 serum and 10 urine samples as duplicates per site; Kaiser will send 12 serum and 12 urine samples as duplicates per site, Yale New Haven and Yale London Ontario will send six (6) serum and six (6) urine samples per site. Because there is no additional sample collection for CLANS, the ASSESS AKI consent/assent does not need to be revised.
- The CLANS study will be conducted at V36M, V48M, V60M, V72M, and V84M. The CLANS cryovials will be shipped using the schedule below:
    - V36M – duplicate will be shipped with regular shipment
    - V48M – duplicate will be shipped with regular shipment
    - V60M – duplicate will be mailed 1 month after the regular shipment
    - V72M - duplicate will be mailed 1 month prior to regular shipment
    - V84M - duplicate will be shipped with regular shipment

8.B Assignment of Participant IDs

- Each CLANS Participant ID will include the Protocol number – Site number-CLANS ID
- We will use the following numbers as Participant IDs:
  - 0301 - 0399 for V36M samples,
  - 0401- 0499 for V48M samples,
  - 0601- 0699 for V60M samples
  - 0701 – 0799 for V72M samples, and
  - 0801 – 0899 for V84M samples.
- Sites will send a file via email on the 15th (or next business day) of each month to the DCC using ASSESS_CLANS alias. This file will be a list of the participants who are scheduled for in-person visits (V36M, V48M, V60M, V72M) for the following month. If the schedule changes or a participant withdraws, the site will notify ASSESS_CLANS within one business day. The DCC will randomly select the participants from the list and assign the CLANS IDs. ASSESS_CLANS will return the list with the CLANS IDs to the site on the 22nd/23rd of each month.
- The DCC will create a log, "CLANS Participant Assignment Log – Visit Number," where the columns are CLANS ID, ASSESS Participant ID, Serum label, and Urine label. The sites will email these logs to ASSESS_CLANS by the 7th of every month so the DCC may verify the assignment of the CLANS IDs from the previous month. This log will link the CLANS ID to the ASSESS Participant ID for analysis and is only available to the individual site and the DCC.

8.C Barcode Labels

- The barcode labels will be provided by the DCC. The DCC will mail the label sheets to the sites before the start of the study. If additional barcode labels are necessary, allow a minimum 5-work-day window for the DCC to generate and ship labels to the sites. CLANS barcodes will include the prefix:
  - AKV for serum
  - AKW for urine
- One duplicate label will be printed for each participant along with a CLANS Participant Assignment Log.

8.D Labeling the Cryovials

1. At the time of processing, one serum cryovial with a barcode label beginning with AKS and location as BIO (Biorepository) will be overlabeled with the CLANS barcode label beginning with AKV and one urine cryovial will be overlabeled with the CLANS barcode label beginning with AKW. The location for all of the CLANS barcode labels is CL (Central Lab). We propose overlabeling to not disrupt the workflow already in place at the sites for processing the ASSESS AKI samples.

8.D.1 Collection Logs for Blood and Urine Aliquots

- The DCC will create a log, "CLANS Participant Assignment Log – Visit Number," where the columns are Participant ID, ASSESS Participant ID, Serum/Plasma label, and Urine label.
    - The sites will email these logs to the DCC by the 7th of every subsequent month so the DCC may verify the assignment of the CLANS IDs from the previous month.
- This log will link the CLANS ID to the ASSESS Participant ID for analysis and is only available to the individual site and the DCC
- Affix the duplicate serum/plasma and urine labels to the appropriate place on the CLANS Participant Assignment Log.
- The original copy of the log(s) will be stored at the clinical center.
- The log can be used by the clinical center for ease in scanning of the barcode for each sample collected.
- On the ASSESS-AKI blood and urine logs make a note next to the record for the sample used for the CLANS study to indicate that it was sent for the CLANS study.

8.D.2 Mock CLANS Participant

- An adult participant is scheduled for V36M.
- Site sends a list of current participants who are scheduled for in-person visits on the 15th of the month
- ASSESS_CLANS forwards the Audit IDs and Participant IDs to the sites on the 22nd/23rd of the month.
- Data collection and collection of blood and urine samples proceeds per ASSESS AKI protocol and Biospecimen MOP.
- Blood and urine samples are processed according to ASSESS AKI Biospecimen MOP.
- One serum sample labeled with AKS barcode with BIO destination is relabeled with an AKV barcode and CL destination label.
- One urine sample labeled with AKU barcode with BIO destination is relabeled with an AKW barcode and CL destination label.
- Duplicate serum and urine labels are affixed to the CLANS Participant Assignment Log V36M.
- Samples are scanned into the Excel document.
- Sites enter Participant ID, Specimen Type, Volume, UOM, Date Collected, Visit, Date Frozen, Comments, and Shipment ID into the Excel document.

- Site sends a printout of the Excel file for CLANS and cc's the ASSESS_CLANS alias.
- Site removes the one serum sample and one urine sample with Biorepository as the destination Lab from the BST and selects "Other" as the reason for the exclusion.
- The Central Lab will mark the Shipment Received.
- Central Lab measurements will be received by the DCC in the scheduled data dump. The results will not appear in the Reports; they will be saved to a data table for retrieval at time of analysis.
- Sites may or may not receive a fax of results with CLANS IDs.

*8.E **Timeline***

- The DCC bypasses the BST for this audit, and uses a SAS-based system, in order to begin the audit as soon as possible. This will conserve time at the site level by minimizing training and BST data entry. If issues arise related to collection, processing, and shipping, the DCC will refer to the ASSESS AKI collection and processing forms and shipment logs.
- The DCC anticipates beginning CLANS in January 2017. The coordinators will forward the list of upcoming participant visits to ASSESS_CLANS on December 15, 2016.

8.F Instructions for CLANS Shipment to the Central Laboratory

8.F.1 Shipping Samples to Central Laboratory

- Ship frozen samples to the central laboratory according to the shipping schedule outlined in section 8.A.
- The Central Laboratory will provide the following shipping supplies:
- Frozen Sample Shipment
  - Insulated Shipper
  - Specimen Boxes
  - Plastic Bags
  - Absorbent Sheets
  - Preprinted FedEx airbill
  - Dry ice label
  - Exempt Human Specimen label
  - In addition to the supplies listed above, you will need:
  - Five pounds dry ice (2.25 kg)

8.F.2 Assembling Frozen Sample Shipments to the Central Laboratory

14. Place the CLANS 2mL cryovials into the ASSESS specimen box. When packing vials, place them in the specimen boxes left to right, top to bottom. Group vials together by patient and visit.
15. Place each specimen box and an absorbent sheet inside a plastic bag. Seal the bag.
16. Place packed cell aliquots in separate plastic bag with an absorbent sheet and seal the bag.
17. Place a layer of dry ice pellets on the bottom of Styrofoam shipping box. Place plastic bag with box of aliquots on top of dry ice layer. Place bag of packed cell aliquots beside the specimen box, on top of dry ice layer. Place additional dry ice pellets on top of specimens. Use at least five pounds (2.25 kg) of dry ice in each shipping box.
18. Place lid on the Styrofoam box. Place the ASSESS shipping logs and the CLANS Excel spreadsheet on top of Styrofoam cover.
19. Close and tape the outer cardboard box.
20. Affix a dry ice label on the side of the shipping box. Enter the weight of dry ice on the label.

21. Affix the "Exempt Human Specimens" label to the side of the shipping box, near the dry ice label.
22. Note to Canadian sites: Add the following statement to your commercial invoice form "These samples are for research use only. They have no commercial value and are supplied free of charge".
23. Use the pre-printed FedEx airbill to ship specimens to the Central Laboratory. (University of Minnesota Medical Center, Fairview)
    a. Section 1: Fill in the date, your name, phone number and return address.
    b. Section 6: Special Handling: Check "Yes, Shipper's Declaration not required". Check the "Dry Ice" box; enter "1" and the weight of dry ice.
    c. Section 7: Enter "1" under total packages and the total weight of the package.
    d. Follow the peel-and-stick instructions on the back of the airbill. As shown, affix the airbill to the top of the box.
24. Call Federal Express at 1-800-GO-FEDEX (1-800-463-3399). Give them the account number on the preprinted FedEx airbill (in section 7, Payment) and your pickup address. FedEx will dispatch a courier to pick up the package. Please schedule shipments Tuesday through Wednesday. Do not ship samples on Mondays, Thursdays, and Fridays.
25. Send a shipment notification to the central lab via email with the ASSESS export data file and CLANS Excel spreadsheet and copy the ASSESS_CLANS on the day the package is picked up by FedEx. You will receive an email notification from the Central Laboratory within 2 business days of receipt of the samples.
26. Contact the Central Laboratory regarding questions about packaging and shipping.

ASSESS AKI

ASsessment,
Serial Evaluation, and
Subsequent Sequelae in AKI
NIH/NIDDK

Equipment Manual of Procedures (MOP)

Version:

December 2015

1 EQUIPMENT TABLE

Site	Height	Weight	BP
Kaiser	Clinic visits: Perspective Enterprises Model No. PE-WM-60-84 Home visits: SECA 217 Road Rod portable stadiometer	UC-321 PL High Capacity Telemedicine Scale	Omron HEM-907XL
Vanderbilt	UC-321 PL High Capacity Telemedicine Scale		Omron HEM-907XL
Yale	SECA 217 Road Rod portable stadiometer	UC-321 PL High Capacity Telemedicine Scale	HEM705CPN
London	SECA 217 Road Rod portable stadiometer	UC-321 PL High Capacity Telemedicine Scale	HEM705CPN
Washington	Healthometer – home visits SECA 213 and Scaletronix– clinic visits		Omron BP 785 – home visits Omron HEM-907XL
Montreal (peds)	SECA 217 Road Rod portable stadiometer*	UC-321 PL High Capacity Telemedicine Scale TANITA Model 1583	Dinamap ProCare 100
Cincinnati (peds)- No home visits	Ayrton Model S100	ST Scaletronix (children) Scale-tronix 4802 (infants)	Dinamap GECarescape V100

2 OMRON HEM-907

2.A Notes on safety

- If inflation cuff does not stop, remove cuff and pull air tube from the main unit.
- If battery fluid gets in your eye or comes in contact with your skin, wash area with water repeatedly and consult a doctor.
- Do not wrap the cuff over IV site or if contraindicated.
- Do not connect air tube or cuff to equipment that is connected to an intracorpeal organ. Air embolisms can result.
- Do not use the unit near flammable gas or anesthetics, in a high pressure oxygen room or oxygen tent.
- Do not touch AC adapter with wet hands.
- Unplug the unit when unused for long periods of time or when cleaning, installing, or removing the unit.
- Confirm readings with a stethoscope when an irregular pulse wave is displayed or if measurement is questionable.
- Use an AC adapter indicated for us with a power supply of 110 VAC.
- Do not share an electric outlet with other unit or appliance.
- After cleaning unit, let dry before plugging in.
- If the unit fails, DC use, turn off, unplug AC adapter from outlet, and contract OMRON repair department.
- Do not disassemble or modify this unit.
- Do not use any cuff other than the models exclusive for this unit.
- Do not use this cuff on infants.
- Do not use this unit on participants using a pump oxygenator.
- Do not use an AC adapter or battery pack not specified for this unit.
- Do not use a cellular phone near this unit.
- Do not use unit in vehicle.
- Do not use in vehicle.
- Do not use broken or damaged power cord.
- Check the unit operation on a regular basis.

2.B Features and functions

- Refer to pages 10-13 in the OMRON Instructional Manual for feature and function pictorials.

2.C About the cuff

- Do not inflate the cuff without wrapping it around the arm.
- Do not use damaged cuff.
- Check the following:
  - Bladder is correctly installed in cuff
  - Bladder is not twisted
  - Bladder tube is protruding from the cuff
- Connect air tube to bladder and machine at base air connector.
- See page 14 of the OMRON Instructional Manual for example pictures.

2.D How to apply the cuff

- Select the cuff appropriate for the participant
- Have the participant place his right or left hand palm facing upward.
- Align the ART. Mark with arrow on the cuff with the brachial artery.
- Wrap the cuff around arm and Velcro ½-1 inch above elbow joint.
- Only 1 finger should be able to slide under the cuff.
- Keep the cuff at heart level during measurement.

Arm Circumference	Name of the Cuff
(7”-9”) 17-22cm	HEM-907-CS19 (Small)
(9”-13”) 22-32cm	HEM-907-CR19 (Medium)
(13”-17”) 32-42cm	HEM-907-CL19 (Large)
(17”-20”) 42-50cm	HEM-907-CX19 (Extra Large)

2.E How to measure blood pressure

- Plug in the machine
- Push the ON/OFF power button to turn on machine.
- Select the single mode on the mode selector dial.
- Set the P-SET know to AUTO (inflation level).
- Put appropriate size cuff on participant
- Push the start button.
- The measurements should be displayed on screen once completed.
- Once done turn off the machine with the ON/OFF button.
- Unplug unit when done.

2.F Care of the unit

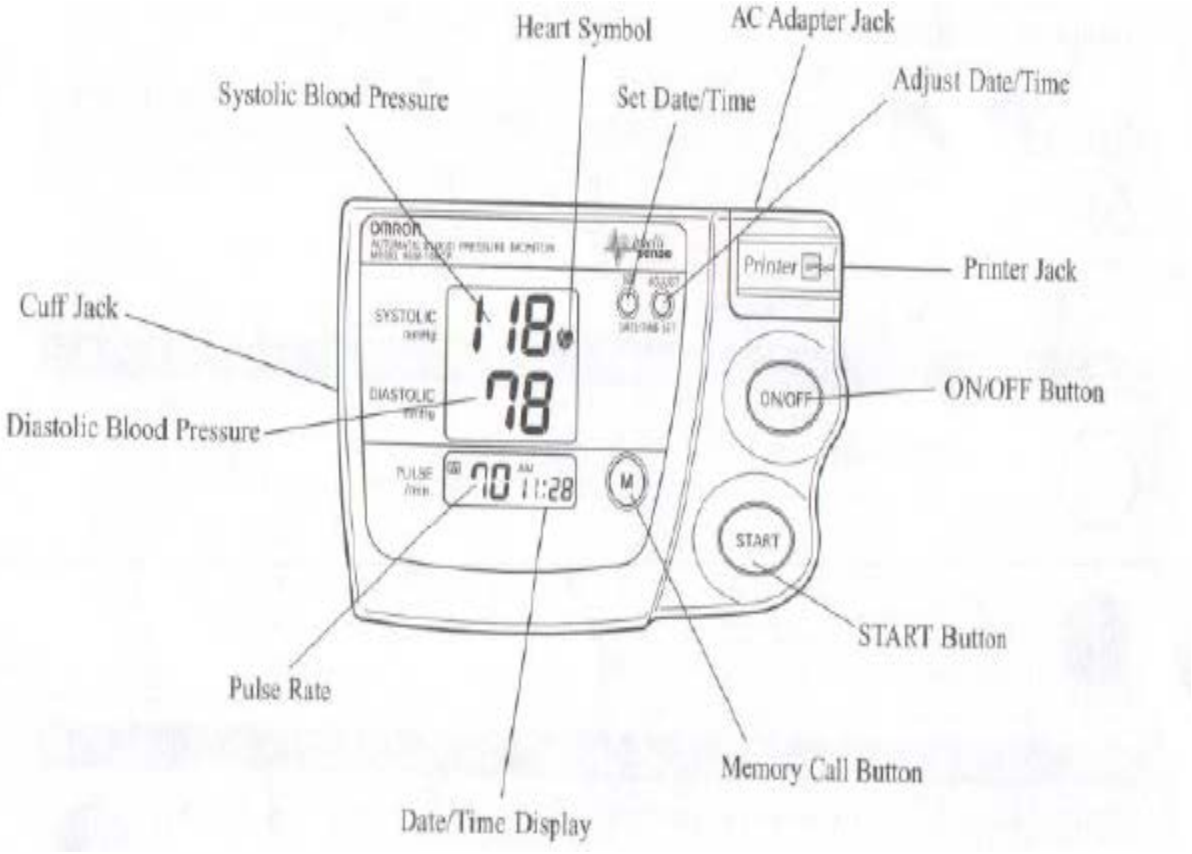
- Make sure the machine is off and unplugged.
- Wipe the monitor with a soft damp cloth diluted with disinfectant alcohol.
- Then wipe with a soft, dry cloth.
- For trouble shooting, see list of error codes on pages 28-29 of the OMRON Instructional Manual.

3 OMRON HEM-705CPN

3.A Notes on safety

- Self-diagnosis of measured results and treatment are dangerous. Please follow the instructions of your physician.
- Do not use the unit on infants or persons who cannot express one's intention.
- Do not use the unit for any purpose other than measuring blood pressure
- Do not use a cell phone near the unit. Improper operation may result.
- Do not disassemble, repair or remodel the main unit or the arm cuff of the blood pressure monitor.
- The battery liquid may leak and damage the main unit. Please observe the following guidelines.
    - When the unit is not being used for a longer period of time (three months or more) take out the batteries.
    - Replace the worn batteries with new ones immediately.
    - Do no use work and new batteries together.
    - Do no insert the batteries with their polarities in the wrong direction.
- Do not force to bend the arm cuff or the air tube excessively.
- When removing the air tube, pull at the connector.
- Do not apply strong shock or drop the main unit.
- Do not inflate the arm cuff without it being wrapped on the arm.

3.B Know Your Unit



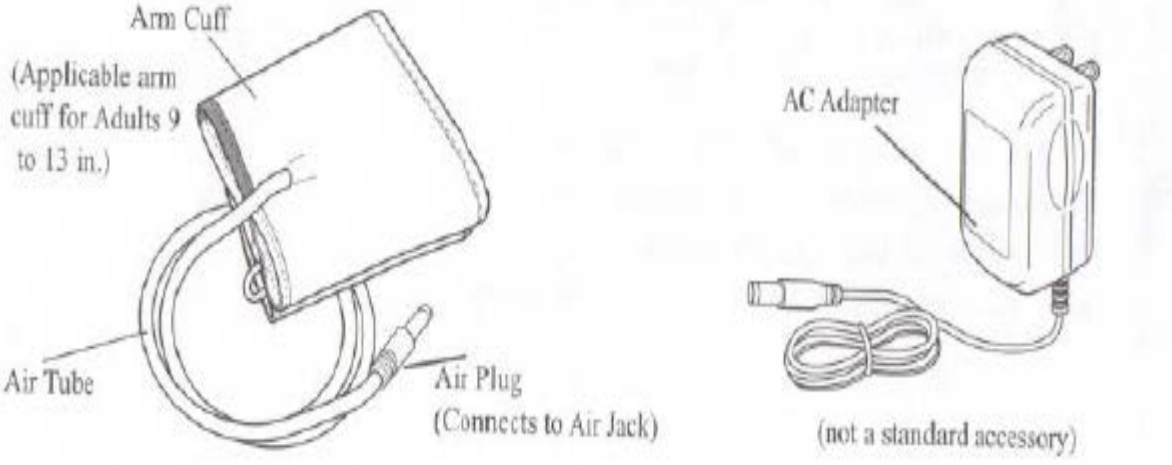
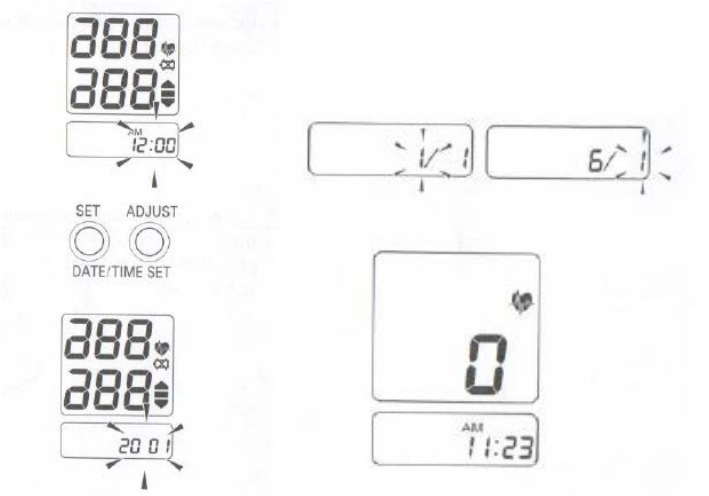


Figure: Accessories

3.C How to Set the Time and Date

- When the batteries are installed, the display will show 12:00AM.
- Press and hold the SET button. The year digits 2001 will flash.
- Press the ADJUST button to advance the digits one at a time. If you hold down the ADJUST button, the digits will advance rapidly.

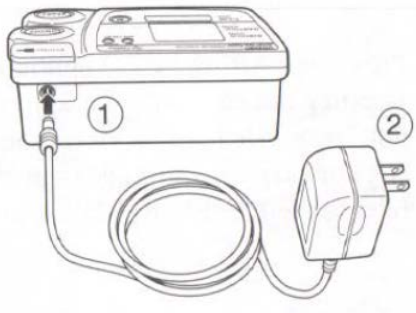


- Press the SET button when desired number is on the display to lock the setting.
- Repeat steps 3-4 for month and date.
- Repeat steps 3-4 for hour and minutes.

3.D How to Use the Optional AC Adaptor

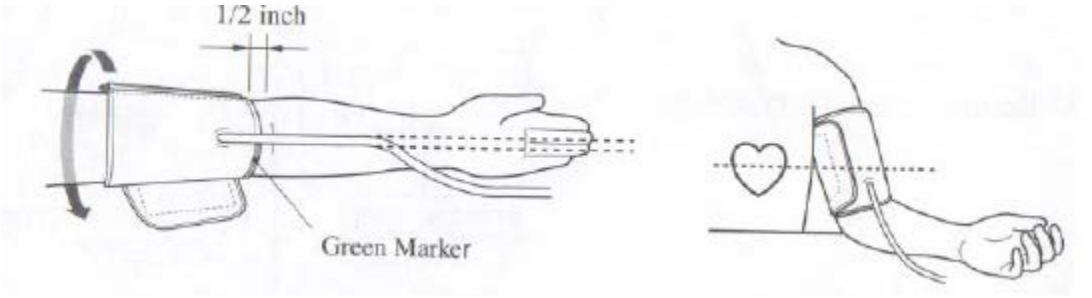
To avoid potential damage to the monitor, use only the exclusive AC adapter (Model HEM ADPT1)

- To connect the AC adaptor insert the AC adaptor plug into the AC adaptor jack on the back of the main unit. Then plug the AC adapter into a 120V AC outlet (50-60 cycles).
- To remove the AC adaptor, disconnect the AC adaptor plug from the AC outlet first and then disconnect the cord from the monitor's jack.
- The monitor is designed NOT to draw power from the batteries when the AC adaptor is in use.



3.E Quick Reference Guide

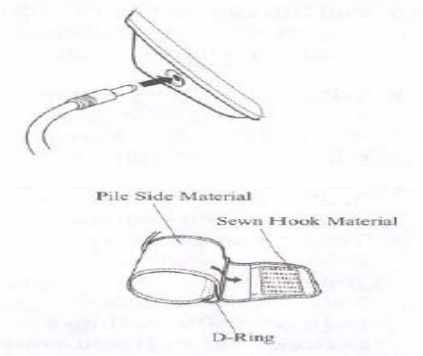
- Avoid eating, smoking and exercising for at least 30 minutes before taking a measurement.
- Remove tight-fitting clothing from your upper arm.
- Sit in a chair with your feet flat on the floor and place your arm on a table so that the cuff is at the same level as your heart.
- Put your arm through the cuff loop making sure that the bottom edge of the cuff is approximately one-half inch above the elbow and that the Green Marker on the cuff is above the brachial artery.



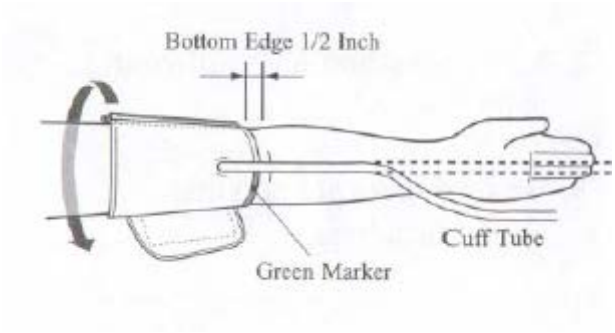
- Pull the end of the cuff so that the entire cuff is evenly tightened around your arm and press the hook material firmly against the pile side of the cuff.
- Press the ON/OFF button.
- After the Heart Symbol appears on the digital panel, press the Start button and remain still until the measurement is complete.
- When measurement is complete, the monitor displays your blood pressure and pulse rate, and automatically deflates the cuff.
- Wait 2-3 minutes before taking another blood pressure measurement. You may require more rest time between readings depending on your individual physiological characteristics.

3.F How to Apply the Arm Cuff

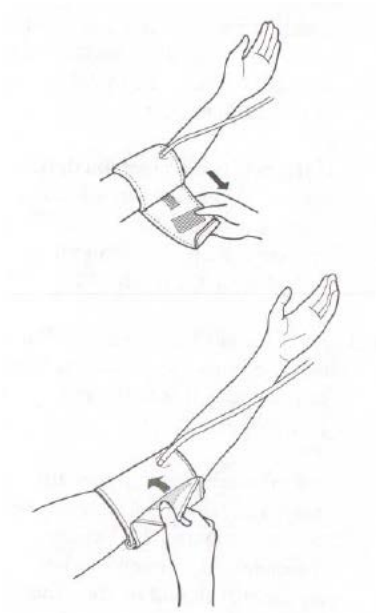
- When the cuff is assembled correctly, the hook material will be on the outside of the cuff loop and the metal D-ring will not touch the skin.
- If the cuff is not assembled, pass the end of the cuff furthest from the tubing through the metal D-ring to form a loop. The smooth cloth should be on the inside of the cuff loop.

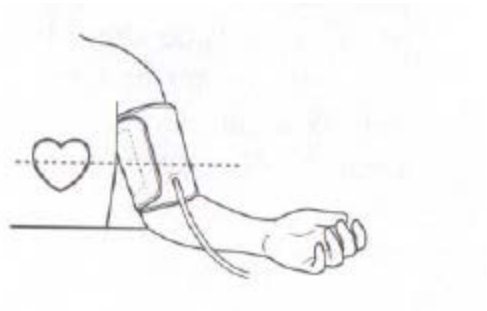


- Sit in a chair with your feet flat on the floor and place your arm on a table so that the cuff is at the same level as your heart.
- Put your arm through the cuff loop. The bottom of the cuff should be approximately 1/2" above the elbow. The Green Marker on the cuff should lie over the brachial artery on the inside of the arm. Tube should run down center of the arm approximately even with the middle finger.



- Pull the cuff so that the top and bottom edges are tightened evenly around your arm.
- When the cuff is positioned correctly, press the sewn hook material FIRMLY against the pile side of the cuff.
- Make certain the cuff fits snugly around your arm. The cuff should make good contact with your skin. You should be able to fit you index finger between the cuff and your arm easily, so you can pull the cuff on and off.

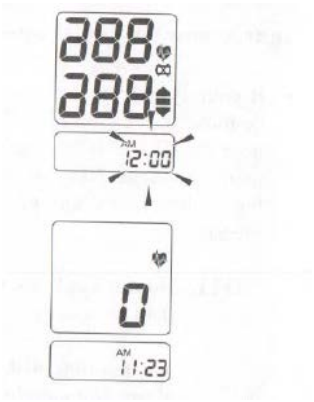




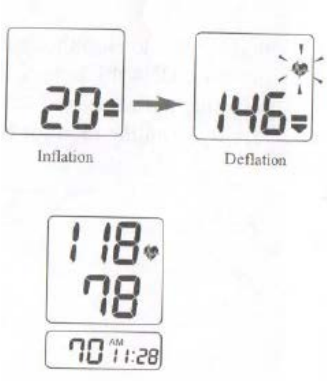
- Relax your arm and turn your palm upward.
- Be sure there are no kinks in the air tubing.

3.G How to Take a Reading

- Press the ON/OFF button.
  - All display symbols appear for approximately one second.
  - When the monitor becomes ready to measure, the Heart Symbol appears on the display.



- Press the START button and remain still.
  - As the cuff begins to inflate, the monitor automatically determines your ideal inflation level. Because this monitor detects the pulse even during inflation, do not move your arm and remain still until the entire measurement completes.
- Inflations stops automatically and measurement is started.
  - As the cuff slowly deflates numbers appear on the display and the Heart Symbol flashes at every heartbeat. In rare circumstances, a higher inflation may be necessary. In those cases, the monitor re-inflates the cuff up to 30 mmHg higher than initial inflation and restarts the measurement.
- When the measurement is complete, the arm cuff completely deflates and your blood pressure and pulse rate are displayed.

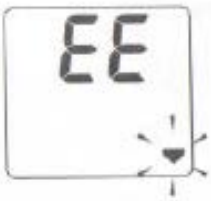
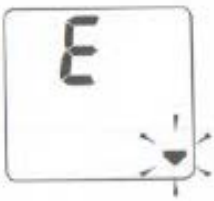
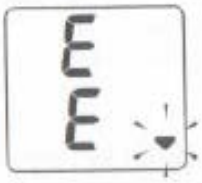
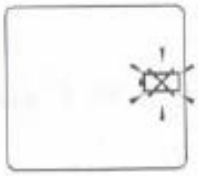


- Press the ON/OFF button to turn the monitor off.
  - If you forget to turn the monitor off, it will automatically shut itself off after five minutes.

3.H How to Take a Reading (Special Conditions)

- If your systolic pressure is known to be more than 220mmHg, push and hold the START button until the monitor inflates 30-40mmHg higher than your suspected systolic pressure.
  - NOTE: do not apply more pressure than necessary.
  - NOTE: the monitor will not inflate above 300mmHg
- If you want to stop the measurement push the ON/OFF button. The monitor will stop inflating and start deflating rapidly, then the monitor will turn off.

3.I Troubleshooting

Error Indicator	Cause	Correction
	Cuff under-inflated.	Turn monitor off, wait 2-3 minutes and take another measurement. Repeat steps listed under "How to Take a Reading." If "EE" is displayed again, take another measurement by pressing and holding the START button as shown on instruction page 12 under "How to Take a Reading", instructions for special conditions. Your cuff maybe wrapped too tightly around your arm.
	Movement during measurement.	
	Cuff over-inflated (more than 300 mmHg).	Turn the monitor off, carefully read and repeat steps listed under "How to Take a Reading."
	Battery voltage is excessively low.	Replace all four "AA" batteries with new batteries.
	Problem caused by abnormal memory function.	Refer to warranty page for sending unit in for repair service.

3.J Care and Maintenance

To protect your monitor from damage, please AVOID the following:

- Subjecting your monitor and cuff to extreme temperatures, humidity, moisture and direct sunlight.
- Folding the cuff and tubing tightly.
- Inflating the monitor over 280mmHg.
- Disassembling the monitor.
- Subjecting the monitor to strong shocks (dropping on the floor).
- Do not clean the monitor with volatile liquids (us e a soft dry cloth to clean the monitor)
- Do not clean the cuff.

4 Omron BP785

Figure: Picture of Omron BP785

4.A Applying the Arm Cuff

The ComFit Cuff is pre-formed for a quick and proper fit for both medium and large sized arms and fits arms 9" to 17".

- Make sure the air plug is securely inserted in the main unit.
- Remove tight fitting clothing from your upper arm.
- Sit on a chair with your feet flat on the floor. Place your arm on a table so the cuff is level with your heart.
- Hold the thumb grip on the cuff securely with your right hand.
- Turn the palm of your hand upward.
- Apply the cuff to your upper arm so the blue stripe is on the inside of your arm and aligned with your middle finger. The air tube runs down the inside of your arm. The bottom of the cuff should be approximately ½" above your elbow.

- Wrap the cuff firmly in place around your arm using the cloth fastener.

  NOTE: Be careful not to rest your arm on the air tube. This will restrict the flow of air to the cuff.

4.B Taking A Measurement

- CALIRBRATION CHECK SYSTEM: When you press the START/STOP button, the Calibration Check System light turns on and the unit starts monitoring your readings using dual sensors. If the unit is accurate and functioning correctly, the Calibration Check System light remains lit during the

measurement. If an error is detected, the Calibration Check System light flashes and "ER" will appear on the display.

CUFF WRAP GUIDE: This monitor checks whether the arm cuff is applied correctly during the inflation. When the cuff is applied correctly,  is displayed while taking a measurement or using the memory function. If the cuff is not applied correctly or movement is detected, an error symbol will be displayed – reapply the cuff and take another measurement.

USER ID: When you select a USER ID the monitor can be set to take one measurement using the single mode or three consecutive measurements (one minute apart) using the TruRead Mode when you press the START/STOP button and displays the average.

4.C For more information

- http://store.omronhealthcare.com/DRHM/Storefront/Company/omrnfit/files/images/product/manual/BP785-IM_012314.pdf

5 DINAMAP GE CARESCAPE V100

Figure: Picture of GE V100 Dinamap

5.A Notes on Safety:

- If inflation cuff doesn't stop, remove cuff and pull air tube from the main unit.
- If battery fluid gets in your eye or comes in contact with your skin, wash area with water repeatedly and consult a doctor
- Do not wrap the cuff over IV site or if contraindicated
- Do not connect air tube or cuff to equipment that is connected to an intracorpeal organ. Air embolisms can result
- Do not use the unit near flammable gas or anesthetics, in a high pressure oxygen room or oxygen tent.
- Do not touch AC adapter with wet hands
- Unplug the unit when unused for long periods of time or when cleaning, installing, or removing the unit
- Confirm readings with a stethoscope when an irregular pulse wave is displayed or if measurement is questionable
- Use an AC adapter indicated for us with a power supply of 110 VAC
- Do not share an electric outlet with other unit or appliance
- After cleaning unit, let dry before plugging in
- Do not disassemble or modify this unit
- Do not use any cuff other than the models exclusive for this unit
- Do not use this cuff on infants
- Do not use this unit on participants using a pump oxygenator
- Do not use an AC adapter or battery pack not specified for this unit
- Do not use a cellular phone near this unit
- Do not use in vehicle
- Do not use broken or damaged power cord
- Check the unit operation on regular basis

5.B Features and Functions

- Refer to owners instruction manual for feature and function pictorials

5.C About the Cuff

- Do not inflate the cuff without wrapping it around the arm
- Do not use damaged cuff
- Connect air tube to bladder and machine at base air connector

5.D How to apply the Cuff

- Select the cuff appropriate for the participant
- Have the participant place his right or left hand palm facing upward
- Align the ART. Mark with arrow on cuff with the brachial artery
- Wrap the cuff around arm and Velcro ½ - 1 inch above elbow joint
- Only 1 finger should be able to slide under cuff
- Keep cuff at heart level during measurement

5.E How to measure blood pressure

- Push the on/off power button to turn on machine
- Put appropriate size cuff on participant
- Push the start button
- The measurements should be displayed on screen once completed
- Once done turn off machine with the on/off button

5.F Care of Unit

- Make sure machine is off and unplugged
- Wipe monitor with soft damp cloth diluted with disinfectant alcohol
- Then wipe with soft, dry cloth

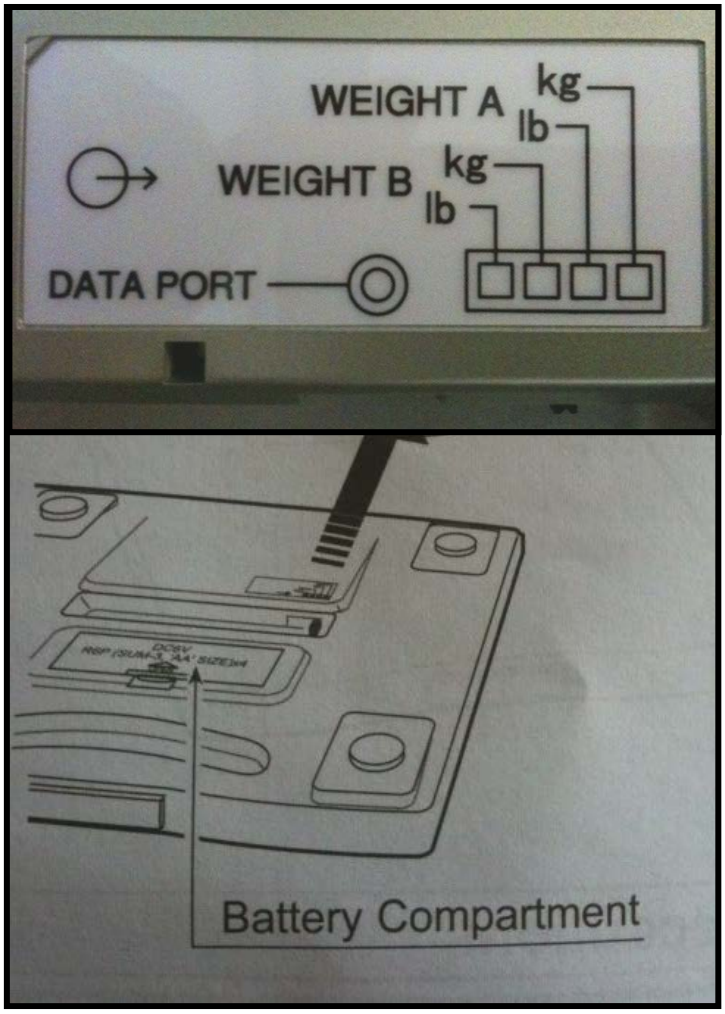
5.G GE Contact Information – USA

Division	Phone #
Applications Support	800-558-7044
Billing/Invoice	877-491-0934
Lease/Loan Financing	800-225-7480
Service: On-Site	800-558-7044
Service: Parts	800-558-7044
Service: Tech Support	800-558-7044
Sales Accessories/Support	800-558-7044
Sales/New Equipment	800-558-5120
Sales: Service	800-552-3248

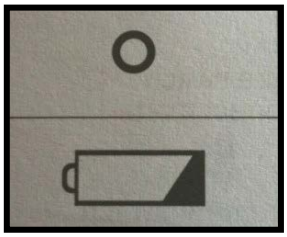
6 UC-321 PL PRECISION HEALTH SCALE

6.A Scale Components

- The Slide Switch can be used to choose between 2 categories:
  - WEIGHT A
  - WEIGHT B
- The difference between WEIGHT A and WEIGHT B is the speed of communication from the data port to another device (e.g. modem, printer, telephone).



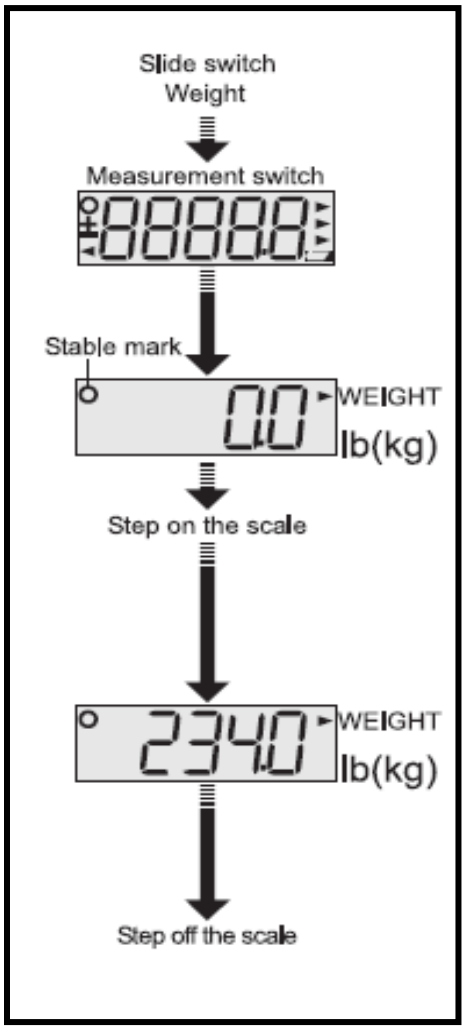
6.B Display symbols



- Ready/complete symbol.
  - Displayed when measurement display is stable.
- Low battery
  - Replace the batteries if displayed.

6.C Measuring weight

- Set the slide switch to the correct mode.
- Press the measurement switch gently.
- Wait until the O symbol appears.
- Weight will be displayed after the O symbol appears.
- Step off the scale.



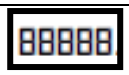
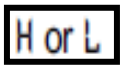
6.D Weight measurement protocol

- Make sure the scale is calibrated before obtaining data measurement.
- Participant should empty bladder.
- Participant can remain in own attire. Remove any excess weight including belts, jewelry, etc.
- Measure weight twice, having the participant step off the scale to repeat zero balance between measurements. The second measurement should be within 0.1 kg of the first measurement. Record the first measurement on form, SEXAM.
- If the difference between the 2 measurements is greater than 0.1 kg, repeat the measurement until 2 results are within 0.1 kg, and record the first of the 2 measurements on form, SEXAM.
- Show participant weight in lbs. upon request.

6.E Maintaining the scale

- Clean the scale with a dry, soft cloth or a cloth moistened with water and mild detergent.
- Remove the batteries if the scale is not going to be used for a long time.
- The scale should be calibrated yearly per ASSESS AKI policy. If the scale is moved on a frequent basis, it should be calibrated more often.

6.F Error messages

Symptoms	Corrective Actions
Nothing is displayed by pressing the measurement switch.	Check the battery installation. Replace batteries.
The indication is fixed to   is displayed.	Remove and reinstall batteries.
There is a large difference between estimated and data measurement.	Place scale on a firm surface. Is something touching the button case?
 or  is displayed.	Replace batteries.

6.G For more information

- Contact:
  - A&D Medical
    1555 McCandless Drive
    Milpitas, CA 95035
    1888-726-9966
    www.LifeSourceOnline.com

7 SCALETRONIX SCALE

7.A For more information

http://scale-tronix.com/pages/productgroup/products/6002wc.html

8 SCALETRONIX 4800 Pediatric SCALE

8.A Operation of the Scale

1. Select a consistent time of day to obtain the weights; for example, early morning, ac, pc, etc.
2. Position the scale in a convenient location. It may be located on a counter top in a central location and plugged in for continuous ON operation, or may be used on a cart and wheeled about, operating on its own internal battery.
3. Prepare scale for weighing. Clean cradle with good quality cleaner, such as "409" or other non-abrasive product. DO NOT CLEAN CRADLE WITH ALCOHOL.
4. Place disposable scale cover or paper on cradle if desired.
5. Prepare the infant for weighing. Remove clothing, dressings, etc., to insure consistency.
6. Turn on scale before placing infant on cradle. This must be done so the computer can sequence through the power-up and automatic zero sequence, and applies to either line power or battery power operation.
7. Be sure scale reads all zeroes before placing infant on scale.
    - For line power use, turn scale on by lifting up on the LINE POWER switch located on the right side panel of the scale near the carrying handle.
    - For battery power (portable) operation, turn scale on by touching the "ON/ZERO" switch on the front panel, maintaining finger pressure for a full second.
8. The "ON/ZERO" switch does two things. It turns the scale on from battery power, and, if the scale is already on, it performs the ZERO function. Should the scale not read zero when empty, simply touch the "ON/ZERO" switch.
9. If extraneous material is to be used on the scale, such as disposable covers, pads, mattress, etc., this material must be placed on the scale before it is turned on, or placed on the scale and the "ON/ZERO" switch pressed to cause the scale to go to zero before placing the infant on the scale.
10. Transfer infant to scale, supporting neck and trunk.
    - Do not place infant on scale until scale is turned on and zeroed.
    - Place infant on cradle.
    - Position infant so the weight is distributed evenly in the approximate center of the cradle.
    - Stabilize infant as necessary with your hand.
    - Remove your hand from the infant, but always keep your hands close in case re-stabilization is required. Do not touch patient while weighing.
11. Read weight when reading stabilizes (three or four seconds after lifting hand).
    - After the weight reading settles down (three to four seconds) you may record it. If it is desired to convert from kilograms to pounds (or vice versa) at any time during the weighing procedure, simply touch the "POUNDS/KILO" touch switch.
      NOTE: All touch switches should be touched in the center of the bordered area between the two words involved. These switches are momentary, alternate action switches, requiring only minimal finger pressure to operate. However, finger pressure must be maintained for a full second so that the switch resets.
    - Movement on any scale will of course cause fluctuation in the weight readings. It is important to stabilize the infant as much as possible, or to mentally average the readings if it fluctuates excessively.
    - If it is desired to HOLD a particular weight reading, simply touch the "HOLD/WEIGH" touch

switch. This will lock the reading into memory and continuously display it (even if the infant is removed from the scale) until the "HOLD/WEIGH" touch switch is pressed again or the scale shuts off.
NOTE: The "HOLD" feature is useful for several applications.

i. It makes it possible to limit the time that the infant is actually on the scale to just a few seconds. It is possible to weigh the infant, wait for a stable reading, and then press the "HOLD/WEIGH" touch switch to lock in the reading. The infant may then be replaced in the bassinet or incubator immediately, without taking the time to chart the weight. After the infant is secure, you may return to the scale to chart the weight. If operating in the battery mode, pressing of the “HOLD/WEIGH" switch will also reset the timer and provide another 80 seconds of ON time before shutting off. When the scale is in this HOLD mode, a "HLD" lighted symbol will blink next to the display. This will alert the operator that the scale is in the HOLD mode.

ii. The HOLD function also facilitates the weighing of an active infant. Wait for the infant to become less active for a few seconds and "capture" or HOLD that weight for charting.

- Dressings may be weighed at some future time after removal, if desired. This weight would then be subtracted from the previous weight reading.

12. Securely grasp infant and remove from scale.
13. After weighing, clean scale again.
14. The scale can be left on continuously when switched on via the line power toggle switch on the right side. This is the preferred method if the scale is to be left in one location all or most of the time. The scale will continuously display zero when empty. If extraneous material is to be used, the "ON/ZERO" switch must be touched each time you wish to zero the scale prior to placing the infant on the cradle.
15. Additional information:
    - Whenever the scale is plugged into a wall receptacle, the battery will be recharging. This is signaled by a "CHG" indicator visible next to the display. This indicates that proper connection has been made to the power line and that the receptacle is "Live".
    - The scale may be operated from the battery either with or without the line power cord plugged in. When not plugged in the cord may be wrapped around the rear handle and the plug tucked in to hold it.
    - Should the battery ever discharge to a level of inaccurate weight, a "LOW BAT' light signal will blink on and off next to the display. This simply means that the battery needs recharging. The scale will still work on line power with a dead battery.
    - There is a 'TEST' toggle switch located on the rear panel of the cabinet near the power cord. It is used for testing the calibration of the scale for service purposes. To use it, simply press it down and hold it for four to five seconds after the scale is on and zeroed. A reading of approximately 1O kg or 22 pounds indicates normal operation. This switch electronically simulates a 10 kg (22 lb) weight. The scale must be indicating all zeroes prior to operating this "TEST' switch.

8.B Calibration Procedure

Your 4800 Pediatric Scale has been carefully calibrated at the factory to an accuracy of 10 grams or better. This calibration involves matching of load cells and readout.

It is recommended that scale calibration be checked semi-annually or sooner if abnormal operating conditions have been experienced. Do not use anything but calibrated scale weights for a thorough scale calibration. Traction weights are NOT acceptable since their weight tolerance can be as high as 10%.

Calibration weights can be obtained from Scale-Tronix or a local scale dealer. We recommend two 10 kg weights for a thorough calibration; one 10 kg weight is the minimum required.

An alternative to calibration weights is a weight comparison method. This requires a calibrated scale with an accuracy of 10 grams or better. A known weight is applied to the calibrated scale; then that same weight is applied to the 4800 Pediatric scale for calibrating.

Since the readout and weight transducers are mounted inside the same cabinet, some disassembly is required to calibrate the scale. Steps to be followed are:

- Remove the plastic weighing cradle by gently lifting straight up.
- Remove the top cover and set aside.
- Carefully disconnect the front panel switch ribbon cable from the display board. It is located under the sloping panel next to the display.
- Remove the entire electronic assembly (PC boards and battery pack). This is done by removing the four screws holding this bracket to the load cell mounting bracket.
- Carefully lift out this assembly and place on bench behind cabinet. The wiring harness has been designed to allow for this temporary repositioning.
- Re-install the weighing platforms.
- Turn on scale by means of line power switch (right side panel).
- After scale indicates all zeroes, place a known accurate weight in the center of the cradle.
- Observe reading. If not accurate, a slight adjustment of the span control located on the analog section may be made.
- Be certain that the cradle is not touching anything and that the wiring harness is not pressing up on the bottom surface of the cradle. Remember this scale is extremely sensitive and any contact or interference will register an error.
- If a slight re-calibration has been accomplished, the TEST signal may need re-setting. With scale indicating all zeroes, press and hold down the rear panel TEST switch. A reading of 10.00 kg is expected. This can be set by adjusting the "CAL" potentiometer located next to the SPAN control.
- The front panel control switches are duplicated on the display board for convenience in troubleshooting.
- The kg or lb startup selection switch is also located on this board. This is a DIP switch that can be used to program this scale to start out in either the kilogram or pound mode when turned on.

8.C Preventative Maintenance

In order to keep your scale in top working order the following preventative maintenance measures are suggested.

- Check calibration semi-annually or as required.
- Inspect weighing cradle for cracks or loose mounting posts (banana plugs).
- Inspect line power cord and plug.
- Replace battery pack annually.
- Store scale in a safe area where it won't be damaged.
- Use the handles for transporting scale.

9 SCALE-TRONIX 4802 Infant SCALE

9.A Operation of the Scale

1. Select a consistent time of day to obtain the weights; for example, early morning, am, pm, etc.
2. Position the scale in a convenient location. It may be located on a counter top in a central location and plugged in for continuous ON operation, or may be used on a cart and wheeled about, operating on its own internal battery.
3. Prepare scale for weighing. Clean cradle with good quality cleaner, such as "409" or other non-abrasive product. DO NOT CLEAN CRADLE WITH ALCOHOL.
4. Place disposable scale cover or paper on cradle if desired.
5. Prepare the infant for weighing. Remove clothing, dressings, etc., to ensure consistency.
6. Turn on scale before placing infant on cradle. This must be done so the computer can sequence through the power-up and automatic zero sequence, and applies to either line power or battery power operation.
7. Be sure scale reads all zeroes before placing infant on scale.
    a. For line power use, turn scale on by lifting up on the LINE POWER switch located on the right side panel of the scale near the carrying handle.
    b. For battery power (portable) operation, turn scale on by touching the "ON/ZERO" switch on the front panel, maintaining finger pressure for a full second.
8. The "ON/ZERO" switch does two things. It turns the scale on from battery power, and, if the scale is already on, it performs the ZERO function. Should the scale not read zero when empty, simply touch the "ON/ZERO" switch.
9. If extraneous material is to be used on the scale, such as disposable covers, pads, mattress, etc., this material must be placed on the scale before it is turned on, or placed on the scale and the "ON/ZERO" switch pressed to cause the scale to go to zero before placing the infant on the scale.
10. Transfer infant to scale, supporting neck and trunk.
    a. Do not place infant on scale until scale is turned on and zeroed.
    b. Place infant on cradle.
    c. Position infant so the weight is distributed evenly in the approximate center of the cradle.
    d. Stabilize infant as necessary with your hand.

e. Remove your hand from the infant, but always keep your hands close in case re-stabilization is required. Do not touch patient while weighing.

11. Read weight when reading stabilizes (three or four seconds after lifting hand).
    a. After the weight reading settles down (three to four seconds) you may record it. If it is desired to convert from kilograms to pounds (or vice versa) at any time during the weighing procedure, simply touch the "POUNDS/KILO" touch switch.

       NOTE: All touch switches should be touched in the center of the bordered area between the two words involved. These switches are momentary, alternate action switches, requiring only minimal finger pressure to operate. However, finger pressure must be maintained for a full second so that the switch resets.
    b. Movement on any scale will of course cause fluctuation in the weight readings. It is important to stabilize the infant as much as possible, or to mentally average the readings if it fluctuates excessively.
    c. If it is desired to HOLD a particular weight reading, simply touch the "HOLD/WEIGH" touch switch. This will lock the reading into memory and continuously display it (even if the infant is removed from the scale) until the "HOLD/WEIGH" touch switch is pressed again or the scale shuts off.

       NOTE: The "HOLD" feature is useful for several applications.

       i. It makes it possible to limit the time that the infant is actually on the scale to just a few seconds. It is possible to weigh the infant, wait for a stable reading, and then press the "HOLD/WEIGH" touch switch to lock in the reading. The infant may then be replaced in the bassinet or incubator immediately, without taking the time to chart the weight. After the infant is secure, you may return to the scale to chart the weight. If operating in the battery mode, pressing of the “HOLD/WEIGH" switch will also reset the timer and provide another 80 seconds of ON time before shutting off. When the scale is in this HOLD mode, a "HLD" lighted symbol will blink next to the display. This will alert the operator that the scale is in the HOLD mode.

       ii. The HOLD function also facilitates the weighing of an active infant. Wait for the infant to become less active for a few seconds and "capture" or HOLD that weight for charting.

d. Dressings may be weighed at some future time after removal, if desired. This weight would then be subtracted from the previous weight reading.

12. Securely grasp infant and remove from scale.
13. After weighing, clean scale again.
14. The scale can be left on continuously when switched on via the line power toggle switch on the right side. This is the preferred method if the scale is to be left in one location all or most of the time. The scale will continuously display zero when empty. If extraneous material is to be used, the "ON/ZERO" switch must be touched each time you wish to zero the scale prior to placing the infant on the cradle.
15. Additional information:
    a. Whenever the scale is plugged into a wall receptacle, the battery will be recharging. This is signaled by a "CHG" indicator visible next to the display. This indicates that proper connection has been made to the power line and that the receptacle is "Live".
    b. The scale may be operated from the battery either with or without the line power cord plugged in. When not plugged in the cord may be wrapped around the rear handle and the plug tucked in to hold it.
    c. Should the battery ever discharge to a level of inaccurate weight, a "LOW BAT' light signal will blink on and off next to the display. This simply means that the battery needs recharging. The scale will still work on line power with a dead battery.
    d. There is a 'TEST' toggle switch located on the rear panel of the cabinet near the power cord. It is used for testing the calibration of the scale for service purposes. To use it, simply press it down and hold it for four to five seconds after the scale is on and zeroed. A reading of approximately 1O kg or 22 pounds indicates normal operation. This switch electronically simulates a 10 kg (22 lb) weight. The scale must be indicating all zeroes prior to operating this "TEST' switch.

9.B Calibration Procedure

Your 4802 Pediatric Scale has been carefully calibrated at the factory to an accuracy of 10 grams or better. This calibration involves matching of load cells and readout.

It is recommended that scale calibration be checked semi-annually or sooner if abnormal operating conditions have been experienced. Do not use anything but calibrated scale weights for a thorough scale calibration. Traction weights are NOT acceptable since their weight tolerance can be as high as 10%. Calibration weights can be obtained from Scale-Tronix or a local scale dealer. We recommend two 10 kg weights for a thorough calibration; one 10 kg weight is the minimum required.

An alternative to calibration weights is a weight comparison method. This requires a calibrated scale with an accuracy of 10 grams or better. A known weight is applied to the calibrated scale; then that same weight is applied to the 4800 Pediatric scale for calibrating.
Since the readout and weight transducers are mounted inside the same cabinet, some disassembly is required to calibrate the scale. Steps to be followed are:

- Remove the plastic weighing cradle by gently lifting straight up.
- Remove the top cover and set aside.
- Carefully disconnect the front panel switch ribbon cable from the display board. It is located under the sloping panel next to the display.
- Remove the entire electronic assembly (PC boards and battery pack). This is done by removing the four screws holding this bracket to the load cell mounting bracket.
- Carefully lift out this assembly and place on bench behind cabinet. The wiring harness has been designed to allow for this temporary repositioning.
- Re-install the weighing platforms.
- Turn on scale by means of line power switch (right side panel).
- After scale indicates all zeroes, place a known accurate weight in the center of the cradle.
- Observe reading. If not accurate, a slight adjustment of the span control located on the analog section may be made.
- Be certain that the cradle is not touching anything and that the wiring harness is not pressing up on the bottom surface of the cradle. Remember this scale is extremely sensitive and any contact or interference will register an error.
- If a slight re-calibration has been accomplished, the TEST signal may need re-setting. With scale indicating all zeroes, press and hold down the rear panel TEST switch. A reading of 10.00 kg is expected. This can be set by adjusting the "CAL" potentiometer located next to the SPAN control.

- The front panel control switches are duplicated on the display board for convenience in troubleshooting.
- The kg or lb startup selection switch is also located on this board. This is a DIP switch that can be used to program this scale to start out in either the kilogram or pound mode when turned on.

9.C Preventative Maintenance

In order to keep your scale in top working order the following preventative maintenance measures are suggested.

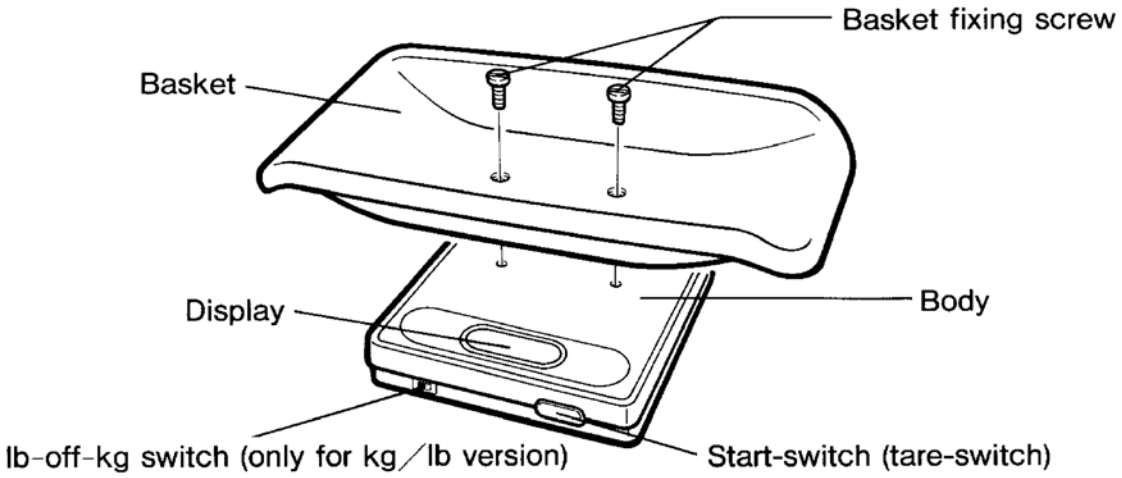
- Check calibration semi-annually or as required.
- Inspect weighing cradle for cracks or loose mounting posts (banana plugs).
- Inspect line power cord and plug.
- Replace battery pack annually.
- Store scale in a safe area where it won't be damaged.

Use the handles for transporting scale.

10 TANITA 1583 BABY SCALE

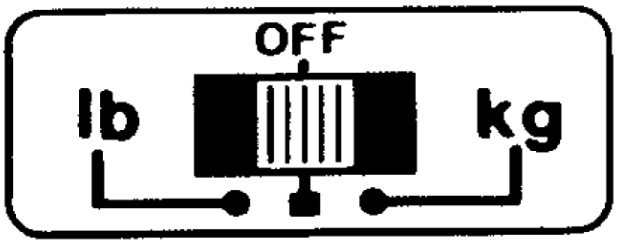
10.A Scale Description

Maximum Capacity	Graduation	Display
40 lb (20 kg)	0-20 lb x 0.5 oz (0-10 kg x 10 g); 20-40 lb x 1 oz (10-20 kg x 20 g)	4 digit 0.9" LED display (21 mm)
Dimensions	**Unit Weight**	**Power Supply**
12.7" x 21.5" x 5.3"	6.2 lb (2.7 kg)	4 x AA batteries



10.B Set Scale to Kilograms

- Turn the power on by sliding the power switch to kilogram.
- The switch is located at the front left hand corner of the scale.
- Display shows 0,00.0 for lb and 0.00 for kg.



10.C Weighing a Baby in kg

- Turn on the scale by sliding the lb-off-kg switch to kg
- Press start-switch to set the scale to 0.00
- Display will show 0.00 (with the kg setting)
- Place the baby on the scale within 60 seconds of pressing the start-switch

- The weight will be displayed
- Take the weight once the number stops changing
- To take multiple weights, press the start-switch between each weight:
    - Remove the baby
    - Press the start switch
    - Wait for the 0.00 to appear
    - Place the baby on the scale
    - Take the weight
    - Repeat
- To close the scale, simply slide the lb-off-kg switch to off

10.D Tare Function

- If a towel or blanket is placed on the scale for hygiene purposes, use the tare function:
    - Turn on the scale by sliding the lb-off-kg switch to kg
    - Press start-switch to set the scale to 0.00
    - Display will show 0.00 (with the kg setting)
    - Place the towel in the tray of the scale
    - Press again the start-switch to set the scale to 0.00
    - Place the baby on the scale within 60 seconds

10.E Error Messages

- LO: low battery
    - Replace the batteries
- OL: over-load
    - Baby or item being weighed is too heavy for the scale. Use a scale with a greater capacity.

11 BAYER CLINITEK STATUS ANALYZER

11.A Loading paper

- Open door in back.
- Move arm to unlock position.
- Thread paper through slots.
- Lock arm.
- Close door.

11.B Powering up

- Push and hold ON button.
- Calibration bar will automatically slide out.
- System will perform a self-test and calibrate.

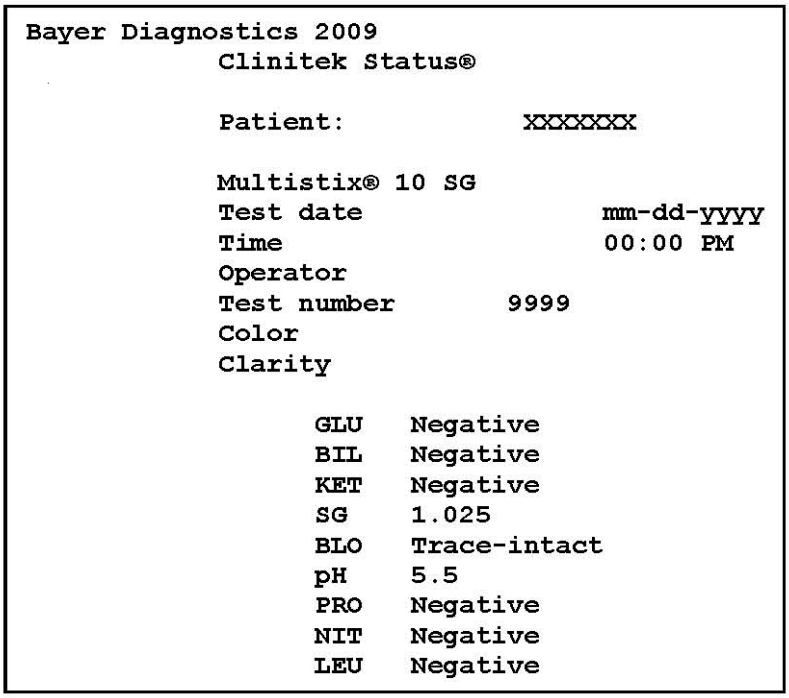
11.C Instrument set up

- Use Start Up Wizard.
- Set Time/Date
- Make sure unit is set for 10SB test strips

11.D Strip test

- Have Ready: Urine, Strip, Blotting Tissue
- Enter Participant ID#
- START:
  - Have only 8 seconds to prepare strip
    - DIP
    - BLOT
    - INSERT
- Test takes 45 seconds until results are displayed.
- PRINT
- DONE

11.E Sample printout



```
Bayer Diagnostics 2009
            Clinitek Status®

            Patient:           XXXXXXX

            Multistix® 10 SG
            Test date                mm-dd-yyyy
            Time                     00:00 PM
            Operator
            Test number       9999
            Color
            Clarity

                  GLU   Negative
                  BIL   Negative
                  KET   Negative
                  SG    1.025
                  BLO   Trace-intact
                  pH    5.5
                  PRO   Negative
                  NIT   Negative
                  LEU   Negative
```

11.F Recalling results

- Any results can be recalled – unit stores them.
- Results are stored in chronological order.

11.G Unit maintenance

- Self-Calibrating
- Cleaning
  - Light cleaning with water
  - Be especially careful with the calibration bar
    - Clean with a Q-tip and water.
- Periodic Control Checks

11.H Ordering supplies

- Sites are responsible for ordering supplies listed below.
- Urine Test Strips
  - Bayer Reagent Strips Urinalysis Multistix 10SG Analytes
    - Bottle of 100 (Fisher Scientific)

    - Approximately $95.00 per bottle.
- Printer Paper
    - Clinitek Thermal Printer Paper
        - 5 rolls/per pack
        - Multiple suppliers – Check on Google
        - Approximately $35.00 per 5 rolls
- Control Checks
    - "The Dipper" Levels 1 and 2 Box – 15 mL
        - Quantimetrix Corporation (VWR)
        - Approximately $160.00

12 SECA 213 STADIOMETER

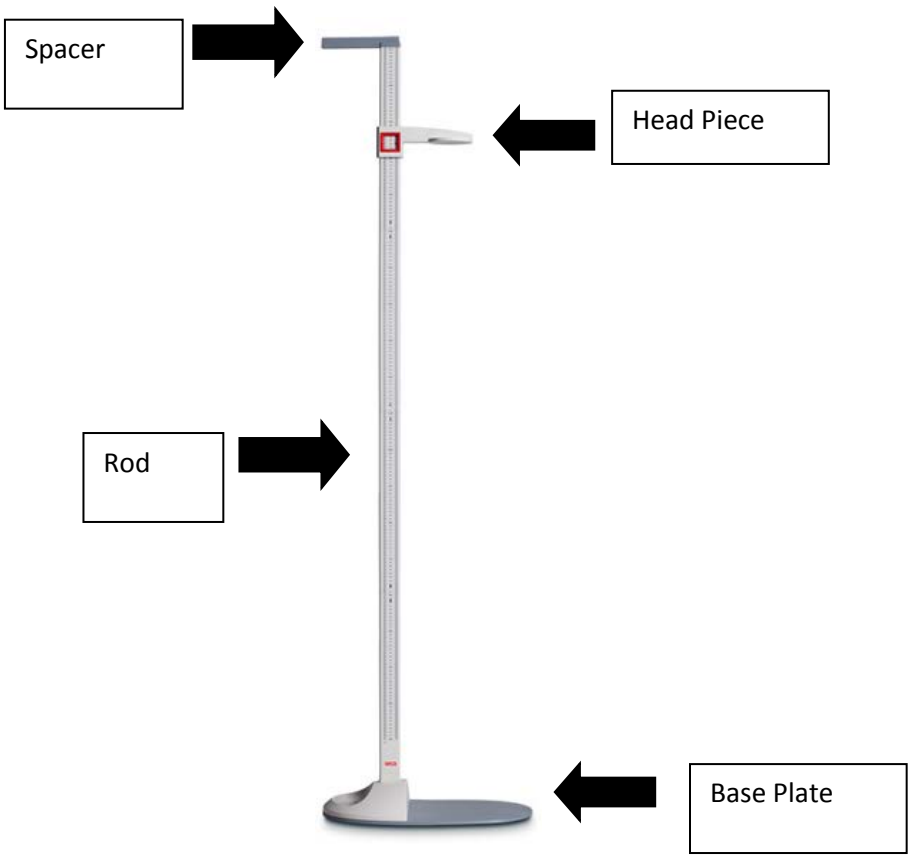
12.A For more information

SECA 213
http://www.seca.com/english/ca/home/products/details/seca/product/height_measuring_instruments_266/seca_213/

13 SECA 217 – STADIOMETER

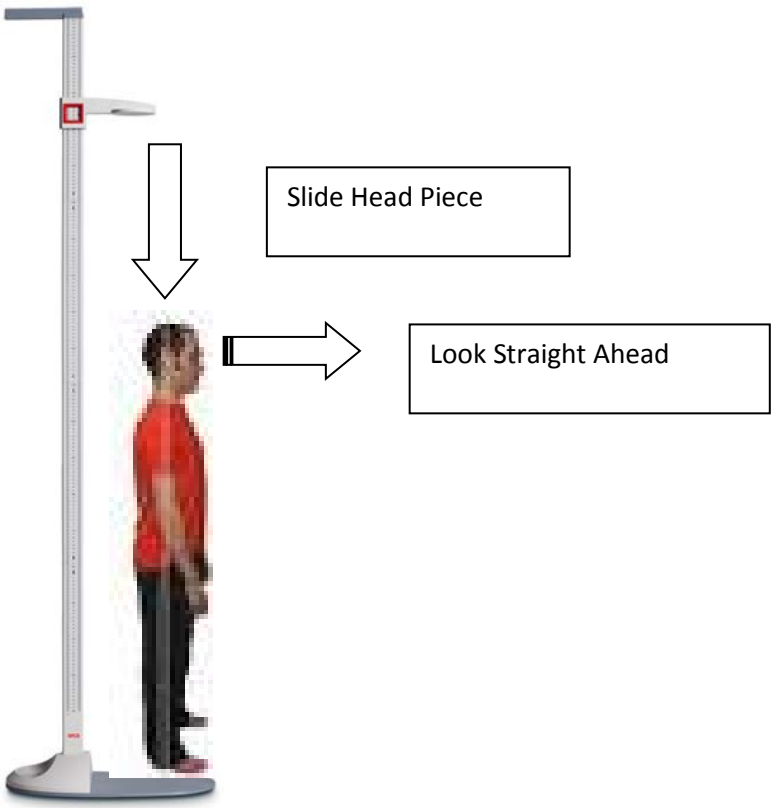
13.A Mounting

- Place the base plate on the floor against a wall.
- Assemble the rod by clicking the first section in the base plate and add subsequent sections by following the order of the scale.
- Slide the head piece on the rod, making sure the head is facing the same direction as the foot rest section of the base plate.
- Attach the spacer on top of the rod pointing towards the wall.
- Please note: The SECA 214 model does not come with a spacer. Therefore, to ensure stability and measurement precision, place the stadiometer against a wall.



13.B Measurement

- Instruct participant to stand on base plate with his back facing the wall.
- Participant must stand straight and look straight ahead.
- Slide the head piece until it touches the head of the participant.
- Read the value on the rod indicated by the red arrow.
- Please Note: Remember to always wipe clean the surfaces in contact with participants with disinfecting products (e.g. 70% ethanol or other).



13.C Technical data

- Measuring Range:
  - 20-205 cm / 8-81”
- Graduation:
  - 1 mm / 1/8”
- Dimensions, stadiometer (WxHxD):
  - 328 x 2.145 x 574 mm
- Device Weight:
  - 3.6 kg

13.D For more information

SECA 217
http://www.seca.com/english/ca/home/products/details/seca/product/height_measuring_instruments_266/seca_217/

SECA 213
http://www.seca.com/english/ca/home/products/details/seca/product/height_measuring_instruments_266/seca_213/

14 PERSPECTIVE ENTERPRISES MODEL NO. PE-WM-60-84 STADIOMETER

14.A Mou*nting*

- Follow instructions and use the Installation and Calibration Device included in the package.

14.B Measurement

- Instruct participant to stand with back to the wall, heels as close to the wall as possible.
- Have participant stand as straight as possible and look straight ahead.
- Slide stadiometer's head piece until it touches the participant's head.
- Record the value indicated by the "Read-Here" mark on the head piece.
- Clean surfaces in contact with participants with alcohol or similarly disinfecting wipes.

14.C Specifications

- Measurement range: 27 5/8 – 84 in; 70 – 213 cm
- Accuracy: 1/8 in; 3 mm
- Assembled Length, Width, Height: 10 x 8 3/4 x 85 in; 25 x 22 x 216 cm
- Weight: 18 lb; 8 kg

14.D For more information

http://www.perspectiveent.com/ssb.html

15 HOLTAIN HARPENDEN STADIOMETER

15.A Contact Information

Tel: 0845 8381976 (Int: +44 1239 891656)
Fax: 01239 393100 (Int: +44 1239 393100)
Crosswell, Crymych, Pembs., SA41 3UF, UK.
Registered in Wales No. 646316

15.B Stadiometer use and Maintenance

- The counter may break if the headboard is 'raced' up or down the backboard. The headboard should therefore be moved to its topmost position when not in use.
    - This should not be moved faster than 30cm/sec
- The stadiometer contains a direct reading counter mounted on a counter-balanced carriage riding on ball bearings. The counter is a self-contained unit and requires no maintenance. A spare counter is provided if replacement should be required.
- The bearings and counter weight pulleys should be lubricated semiannually with one drop of light machine or instrument oil.
- The "formica" covering may be washed with soap and water as required.

15.C Measurement Procedure

- General Issues
    - To perform this measurement accurately, it is important that the recorder observe both the position of the participant and of the stadiometer. The participant should be instructed to avoid slouching and the stadiometer brought down in the midline of the head.
- Administration
    - Have the participant stand with their back against the wall-mounted stadiometer, heels together. The back (scapulae), buttocks and both heels should be touching the wall-plate. Note: the participant should be standing with head erect, but, in general, the back of the head does not need to be in contact with the wall-plate.
    - Check that the participant is in the correct position, starting with the heels and checking each point of contact with the wall-plate.
    - Check that the arms are relaxed and hanging loosely at the sides and that the shoulders are relaxed by running your hands over them and feeling the relaxed trapezius muscle.
    - The head should be in the "Frankfort Horizontal Plane" in which the lowest point on the inferior orbital margin (orbitale) and the upper margin of the external auditory meatus (tragion) form a horizontal line. To verify that the head is in the Frankfort plane, hold the

base of a clear plastic right angle (or T of a T-square) against the wall and make sure that the edge perpendicular to the wall is parallel to the "Frankfort Horizontal Plane."

- Be sure that the participant maintains the correct posture during the measurement. Bring the horizontal bar down firmly onto the top of the head. It may also be necessary, upon occasion, to alter the hair styling of some of the participants for the horizontal bar to make contact with the top of the scalp.
- Record the reading on the stadiometer just before the participant exhales.

16 AYRTON STADIOMETER MODEL S100

16.A Contact Information:

Ayrton Corporation
5322 Frost Point Circle
Prior Lake, MN 55372 USA
Tel: 952-447-4542; 800-888-3840
Fax: 952-447-4548

16.B Stadiometer Use and Maintenance

- The Ayrton S100 Stadiometer accurately measures from 20 to 87 inches. Graduations are marked in millimeters in blue and in sixteenths of an inch in red.
- The Ayrton Height Rod is wall-mounted for stability and accuracy.
- The clear plexi-slide of the Stadiometer makes measurements easy to read; the clear plexi headpiece should allow smooth, binding-free movement under any environmental condition.
- The stadiometer may be washed with soap and water, or by using a sanitizing wipe, as required.

16.C Measurement Procedures

5.1 General issues

To perform this measurement accurately, it is important that the recorder observe both the position of the participant and of the stadiometer. The participant should be instructed to avoid slouching and the stadiometer brought down in the midline of the head.

5.2 Administration

1) Have the participant stand with their back against the wall-mounted stadiometer, heels together. The back (scapulae), buttocks and both heels should be touching the wall-plate. Note: the participant should be standing with head erect, but, in general, the back of the head does not need to be in contact with the wall-plate.

(2) Check that the participant is in the correct position, starting with the heels and checking each point of contact with the wall-plate.

(3) Check that the arms are relaxed and hanging loosely at the sides and that the shoulders are relaxed by running your hands over them and feeling the relaxed trapezius muscle.

(4) The head should be in the "Frankfort Horizontal Plane" in which the lowest point on the inferior orbital margin (orbitale) and the upper margin of the external auditory meatus (tragion) form a horizontal line. To verify that the head is in the Frankfort plane, hold the base of a clear plastic right angle (or T of a T-square) against the wall and make sure that the edge perpendicular to the wall is parallel to the "Frankfort Horizontal Plane."

(5) Be sure that the participant maintains the correct posture during the measurement. Bring the horizontal bar down firmly onto the top of the head. It may also be necessary, upon occasion, to alter the hair styling of some of the participants for the horizontal bar to make contact with the top of the scalp.

(8) Record the reading on the stadiometer just before the participant exhales.

ASsessment,
Serial Evaluation, and
Subsequent Sequelae in AKI
NIH/NIDDK

General Manual of Procedures (MOP)

Version:

April 2020

1 PROTOCOL

2 ADMINISTRATIVE ORGANIZATION AND ROLE OF PARTICIPANTS

2.A Study Overview

2.A.1 Study Design and General Plan

The ASsessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) Consortium includes Clinical Research Centers (CRCs) led by Kaiser Permanente of Northern California, Yale University, Vanderbilt University, and University of Washington as well as a Data Coordinating Center (DCC) at The Pennsylvania State University and representatives from The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The overall goals of ASSESS-AKI are to make significant contributions to the field of AKI in the five following areas:

- Establishing a diverse prospective parallel, matched cohort of adults and children with and without AKI.
- Characterizing the short-term and long-term natural history of AKI based on current serum creatinine-based diagnostic criteria.
- Evaluating the incremental utility of novel blood and urine biomarkers to refine the diagnosis and prognosis of AKI.
- Developing a prognostic risk score that integrates patient characteristics and biomarkers to help inform providers and patients about the risks of adverse events after an episode of AKI.
- Identifying the subset of high-risk patients with AKI who could be targeted for future interventional clinical trials to improve outcomes after an episode of AKI.

2.A.2 Specific Aims and Study Hypotheses

The ASSESS-AKI Consortium will address the following Specific Aims through the initiation and follow-up of a long-term prospective cohort of participants with and without evidence of acute kidney injury (AKI) based on serum creatinine-based criteria:

2.A.2.a Primary Aims and Study Hypotheses

Aim 1. To determine whether hospitalized persons who survive an episode of AKI have a greater risk of developing chronic kidney disease or faster progression of pre-existing chronic kidney disease than hospitalized persons without AKI after accounting for pre-existing level of kidney function and potential confounders.

Hypothesis 1a. An episode of AKI independently increases the risk of incident chronic kidney disease in persons without pre-existing chronic kidney disease.

Hypothesis 1b. An episode of AKI independently increases the risk of faster progression of chronic kidney disease and development of end-stage renal disease (ESRD) in persons with pre-existing chronic kidney disease.

Aim 2. To determine whether hospitalized persons who suffer from an episode of AKI have a higher risk of

death, cardiovascular events, and other adverse events after hospital discharge than matched persons who did not suffer AKI during hospitalization, after accounting for pre-existing level of kidney function and potential confounders.

Hypothesis 2. AKI increases the short- and long-term risks of death from any cause, cardiovascular events, and any other adverse outcomes (e.g., poorer cognitive function, quality of life, or functional status) in persons with and without pre-existing chronic kidney disease, even after adjustment for potential confounders.

2.A.2.b Secondary Aims and Study Hypotheses

Aim 3. To evaluate the incremental value of serial measurements of several different blood and urine biomarkers for predicting short- and long-term clinical outcomes after an episode of AKI currently defined using changes in serum creatinine.

Hypothesis 3. Novel serum and/or urine biomarkers can improve the prediction of clinical prognosis after an episode of AKI using a serum creatinine-based definition.

Aim 4. To assess whether severity and type of the AKI episode and the presence of pre-existing chronic kidney disease influence long-term risks of loss of kidney function, death, and cardiovascular events in persons with AKI.

Hypothesis 4. Greater severity of an AKI episode (presumed acute tubular necrosis etiology), and the presence and severity of pre-existing chronic kidney disease raise the risk of adverse outcomes after an episode of AKI.

Aim 5. To determine if persons who completely recover kidney function within three months of an episode of AKI have a lower risk of adverse events than those persons with AKI whose recovery is incomplete.

Hypothesis 5. Persons who have incomplete recovery of kidney function within three months after an episode of AKI will have a higher risk of adverse clinical outcomes that is mediated primarily through incident and progressive chronic kidney disease.

Aim 6. To develop a risk score incorporating demographic features, clinical factors, and/or biomarkers that accurately predicts outcomes after an episode of AKI.

Hypothesis 6. A clinically useful and easily implementable risk score can be developed that integrates information on individual characteristics and/or serum/urine biomarkers to provide robust prognostic information for individuals who experience an episode of AKI.

2.B Collaborating Groups

2.B.1 Consortium Organization

The organizational structure of the ASSESS-AKI Consortium is summarized in Figure 5. The ASSESS-AKI Consortium consists of a cooperative agreement between NIDDK/NIH, the four Clinical Research Centers (CRCs), and one Data Coordinating Center (DCC). The Consortium has a Steering Committee (SC), which is the main governing body to develop and direct its activities. An External Expert Panel (EEP) provides input to NIDDK regarding the design of the studies and the progress of the Consortium. The ASSESS-AKI Consortium is comprised of ancillary efforts to NIH-funded studies in progress at the four CRCs: TRIBE, an ongoing multi-center study examines timed renal injury after cardiac surgery; VALID, an ongoing ICU-based clinical study of more complex "un-timed" forms of AKI in the setting of severe illness; Kaiser Permanente of Northern California, an ongoing longitudinal study of the epidemiology and outcomes of AKI within a large community-based population involving patients hospitalized in different settings; and the University of Washington joined the Consortium in October 2010 having an intensive care population.

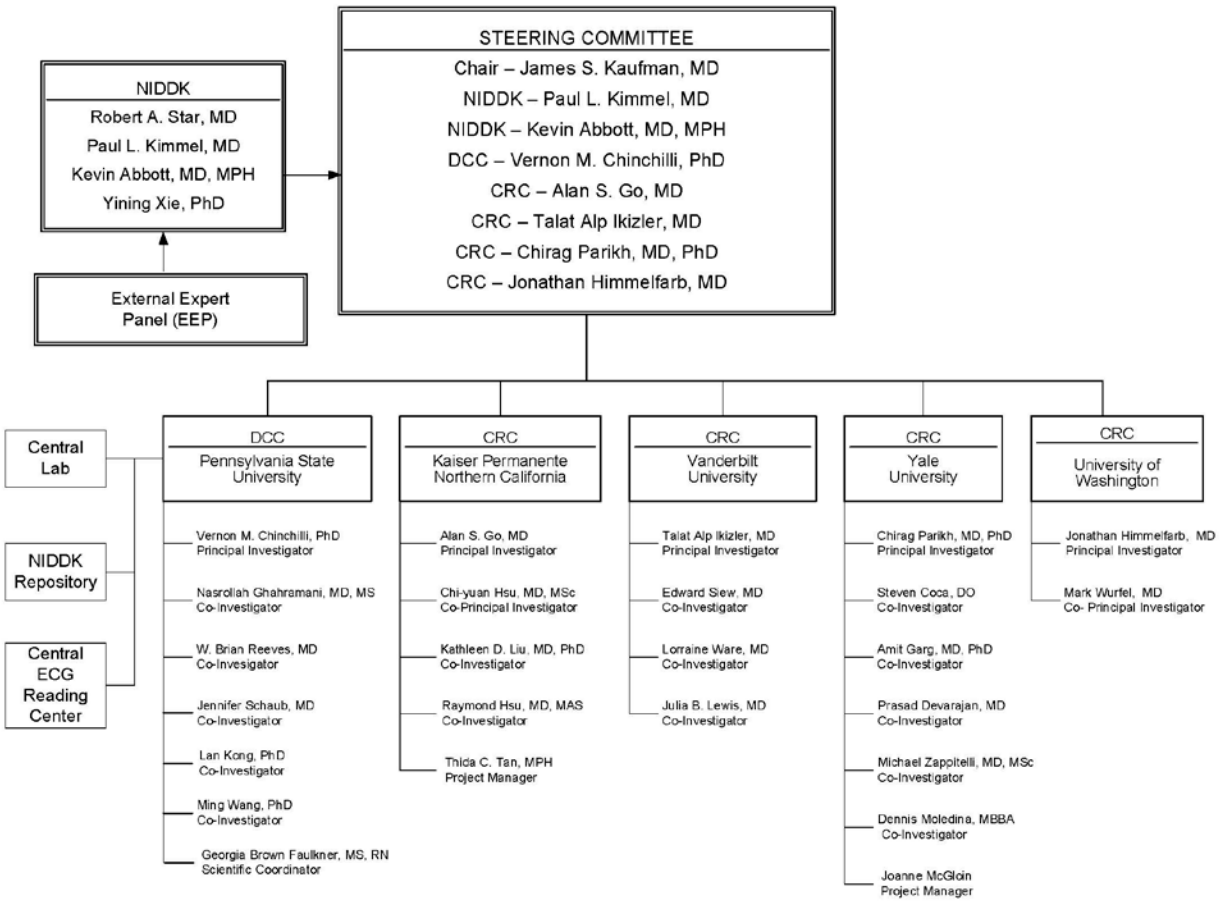


Figure 5. ASSESS-AKI Organizational Chart

2.B.2 Clinical Research Centers (CRCs)

2.B.2.a Yale University - TRIBE-AKI

The study is conducted under the leadership of Dr. Chirag Parikh at Yale University, who is also the PI of the TRIBE-AKI Study. Co-investigators include Drs. Steven Coca, Amit Garg, Jay Koyner, Prasad Devarajan, and Michael Zappitelli and Dennis Moledina, MBBA. The research coordinator is Joanne McGloin and the site statistician is Zhu Wang. All team members are involved in each stage of the research process, and critical interactions are facilitated by bi-weekly scheduled meetings of all key personnel as members of the site SC. Meetings between the Yale investigators and the other PIs at the sites in the existing TRIBE-AKI consortium occur on a monthly basis. In addition, a call between all site coordinators occurs on a weekly basis.

2.B.2.b Vanderbilt University Medical Center - VALID

The study is conducted under the leadership of Drs. Alp Ikizler and Edward Siew. The project was initially started as an ancillary study to the VALID Study and subsequently expanded to all patients admitted to VUMC. Other co-investigators are Drs. Lorraine Ware and Julia B. Lewis. All team members are involved

in each stage of the research process, and critical interactions will be facilitated by bi-weekly scheduled meetings of all key personnel as members of the site SC. During these meetings, personnel update all investigators on key aspects of patient visits, retention, assay quality control, and analysis. Administrative details including scheduling, and ordering of laboratory and office supplies are handled by Dr. Charles Ellis and administrative staff. Dr. Ellis coordinates all data and specimen transfer to the DCC and the NIDDK Biorepository under the supervision of Dr. Ikizler.

2.B.2.c Kaiser Permanente of Northern California

The Kaiser Permanente of Northern California (Kaiser) CRC is an extension of an ongoing collaboration between the Kaiser Division of Research, Departments of Nephrology within The Permanente Medical Group, and the Division of Nephrology at UCSF. The Kaiser CRC is led by Dr. Alan S. Go who will take responsibility for all administrative, protocol, and clinical responsibilities. Dr. Go is supported by Dr. Chi-yuan Hsu at UCSF (Co-PI), and Dr. Kathleen Liu at UCSF (Co-I) who provide complementary content, methodological, and operational expertise, and Dr. Raymond Hsu at UCSF (Co-I). The organization of the Kaiser CRC is summarized in Figure 6 below:

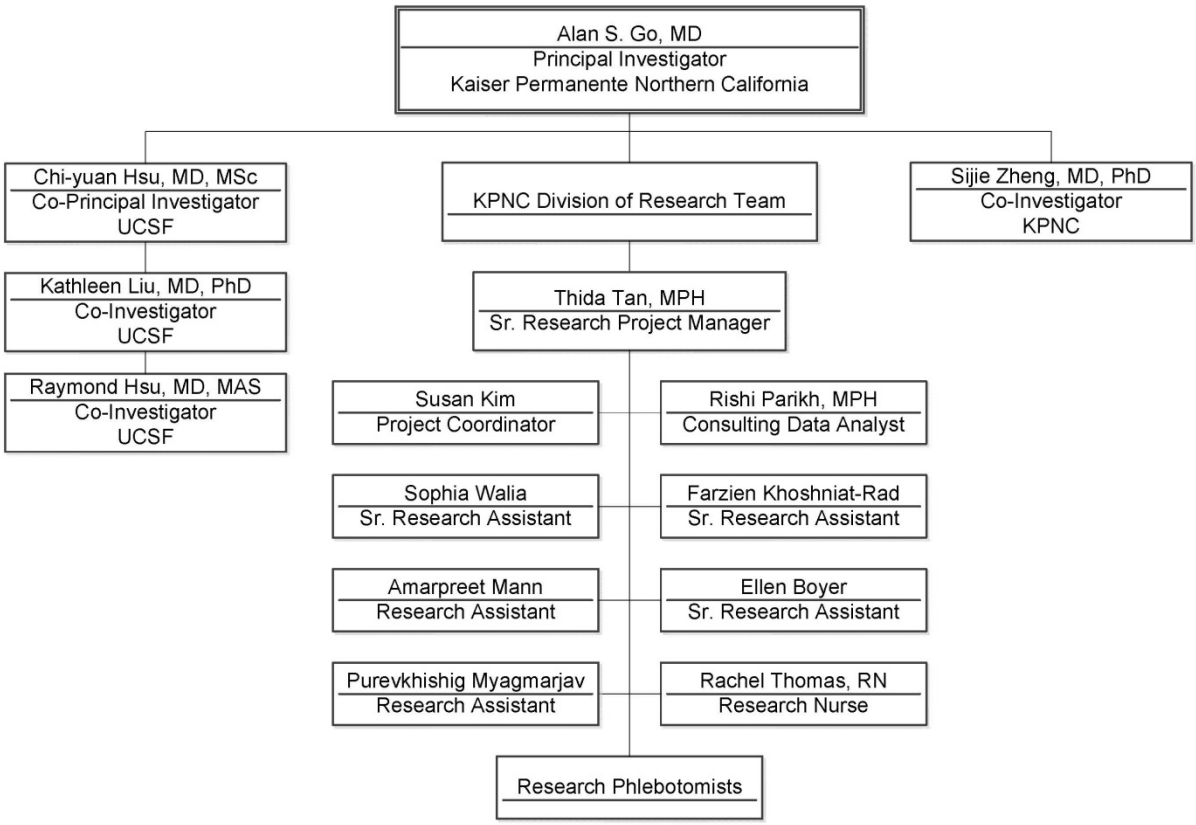


Figure 6. Organizational Structure of the Kaiser Permanente of Northern California CRC

The Kaiser CRC is highly integrated with weekly meetings among the Kaiser study team and monthly meetings among the entire CRC team. In addition, Dr. Go is in frequent e-mail and phone contact with Drs. Hsu, and Liu to address any scientific, clinical, or critical operational issues.

All study protocol elements (administrative and clinical) are implemented through the Kaiser team with overall supervision by Dr. Go. For study components, the Project Manager is supported by the study Project Coordinator, Research Assistants, Data Consultant, and Research phlebotomists.

2.B.2.d University of Washington

This Ancillary study will be under the direction of Jonathan Himmelfarb MD (PI, Nephrology) and Mark Wurfel, MD, PhD (Co-PI, Pulmonary & Critical Care). They will capitalize upon their combined expertise in AKI, CKD, critical care medicine, genetic analyses, and bioinformatics. The study will take advantage of collaborations with two consortiums; an ongoing independent multi-center genome wide association studies consortium in critically ill patients (iSPAAR Consortium), and with a general population consortium (CDGgen Consortium). The consortiums will enable validation and replication of study findings. The study team will also include a Study Coordinator and a Research RN, who will together focus on enrollment, data collection and entry, patient tracking and scheduling, and all other aspects of actualizing a successful study.

2.B.3 Data Coordinating Center (DCC)

The Department of Public Health Sciences (DPHS) and the Division of Nephrology in the Department of Medicine at The Pennsylvania State University College of Medicine, Hershey, serves as the DCC for ASSESS-AKI. Vernon Chinchilli, PhD oversees the DCC as the PI. The Co-Investigators include nephrologists, Nasrollah Ghahramani, MD, MS, W. Brian Reeves, MD, and Jennifer Schaub, MD, and biostatisticians, Lan Kong, PhD and Ming Wang, PhD.

The DCC provides leadership for the biostatistical aspects of optimizing study designs for increased accuracy and precision, projecting sample sizes, selecting and implementing sampling schemes, assisting in defining the primary and secondary outcomes and analytical approaches for the protocols, executing the statistical analyses of study data, serving as a central repository for data generated from the Clinical Research Centers (CRCs), developing the presentations/publications, coordinating sample and data flow between the CRC sites, the NIDDK Central Repository (as of March 2018, Precision for Medicine replaced Fisher and Rutgers), central laboratory (University of Minnesota), ECG reading center (EPICARE), and the Investigators, and preparing the confidential data analyses and reports for the External Expert Panel (EEP) and the NIDDK. The DCC establishes and manages the computer network, a secure and confidential computerized system to collect study data, including cardiac imaging data. The network operates via the Internet and World Wide Web and integrates quality assurance measures and the capability to produce data reports.

The DCC team provides scientific coordination for the CRCs, which includes collaborating with the ASSESS-AKI investigators on protocol development and implementation; overseeing the informed consent process; preparing and leading the training sessions; overseeing quality control site visits; and establishing the certification criteria for ASSESS-AKI procedures. The DCC assumes primary responsibility for

preparing the reports, presentations, and publications. The DCC identifies, secures, and provides appropriate oversight to the subcontracts for Central Laboratories and other adjuncts to the study on behalf of ASSESS-AKI; administers systems for sample collection, distribution, tracking, and storage of biological specimens, ECGs, and cardiac images. The DCC provides project management and administrative support that includes developing an effective organizational structure; facilitating orientation of all members; tracking project timelines and resources; coordinating the conferences, meetings, and presentations; and providing logistics and editorial and clerical assistance with publications. The DCC also leads the Consortium in addressing analytic issues.

The DCC coordinates activities of the committees, which includes at a minimum, Steering, Quality Control, Coordinator, Biomarker Partners, Ancillary Studies, Event Adjudication, and Publications and Presentations. The DCC assumes administrative responsibility for responding to the funding and regulatory agencies. The DCC provides recruitment support and tracking to the CRCs, working with the CRCs to tailor the most effective recruitment strategy. Based on the eligibility criteria determined by the SC, the recruitment strategies are regularly monitored, modified, and updated for consistency.

2.B.4 Core Measurement Laboratory and Reading Centers

The DCC serves as the Consortium liaison to external entities, such as a central laboratory and pharmaceutical and biotechnology companies. The DCC establishes, via subcontracts, central and partner laboratories and reading centers, as deemed necessary by the study protocol. It provides administrative coordination for the storage, retrieval, processing, and testing of biological specimens obtained from cohort study participants.

3 CONSORTIUM COMMITTEES

3.A Steering Committee (SC)

3.A.1 Purpose

The Steering Committee is the main governing body of the Consortium.

3.A.2 Membership

The seven voting members include the Principal Investigators (PI) of the Clinical Research Centers (CRCs), the PI of the Data Coordinating Center (DCC), the Study Chair, and the Project Scientist from the NIDDK. Co-Investigators and other officials from the National Institutes of Health (NIH) NIDDK may participate in SC activities, but they are not SC members and do not have voting privileges. The Study Chair is appointed by the NIDDK and is not a PI of one of the CRCs.

Chair:
NIDDK:
DCC:
Kaiser:
Vanderbilt:
Yale:
University of Washington:

3.A.3 Responsibilities

The Study Chair plans Consortium activities, oversees its functions, conducts SC meetings, and casts tie-breaking votes in that committee. The SC will develop and ensure compliance with ASSESS-AKI Consortium policies and procedures, identify and prioritize strategies for investigation, evaluate protocols proposed by the CRCs, and develop common protocols for submission to the EEP for approval. The SC will ensure that studies are properly conducted and monitored, that data are appropriately analyzed and interpreted, and that study results are reported in the scientific literature in a timely manner. The SC may meet in-person as often as three to four times in the first 12 months of the study, and two to three times per year thereafter. All major scientific decisions will be determined by majority vote of the SC.

The SC convenes weekly via teleconferences and meets at least quarterly to accommodate the timely development of protocols in the Baltimore MD/Washington DC area. The SC operates with standing committees and subcommittees as needed to enhance its effectiveness and includes at a minimum:

- Quality Control Committee
- Biomarker Partners Committee
- Forms Committee, which transitioned into the Coordinators Committee
- Subcommittees
  - Ancillary Studies
  - Event Adjudication Committee

- Publications and Presentations Committee
- Other Committees may be constituted as needed

3.B Quality Control Committee (QCC)

3.B.1 Purpose

The QCC develops the standards for data collection, procedures, and laboratory tests used in ASSESS-AKI and evaluates appropriate adherence to them during performance of each protocol.

3.B.2 Membership

Voting members include one to two representatives from each CRC and the DCC. Other SC members and invited personnel may participate, but they do not have voting privileges unless the QCC decides otherwise. Chair of the QCC is one of the Principal Investigators, who is selected by the QCC.

Chair:
NIDDK:
DCC:
Kaiser:
Vanderbilt:
Yale:
University of Washington:

3.B.3 Responsibilities

The QCC is responsible for assuring quality control for each study protocol. Specific responsibilities include but are not limited to: reviewing and approving standard data forms; recommending certification requirements for study personnel; overseeing event adjudication; monitoring CRC performance using quality metrics developed in coordination with the DCC; recommending changes to improve implementation and performance; reviewing protocol violations; analyzing and interpreting data (including participation in chart reviews); and for making recommendations for site visits when problems are identified, with ad hoc reviewers as indicated. All quality assurance questions and problems will be addressed to the QCC, who in turn will report to the ASSESS-AKI SC.

3.C Forms Committee/Coordinator Committee

3.C.1 Purpose

The Forms Committee develops the standard data collection forms for adult and pediatric participants for review and approval by the QCC. Chair of the Forms Committee is the DCC Scientific Coordinator

3.C.2 Membership

Forms Committee membership consists of the DCC team (Scientific Coordinator and Data Management and Research Computing representatives), at least one coordinator from each CRC, and CRC site investigators.

3.C.3 Responsibilities

Responsibilities include developing standard data collection forms, pilot-testing the pre-approved forms using chart reviews and interviews, proposing form changes, and presenting the forms to the QCC for review and approval.

3.C.4 Transition to Coordinator Committee

The Forms Committee transitioned into the Coordinators Committee once the forms were finalized.

3.C.4.a Purpose

The Coordinators Committee will serve as a forum to review any protocol, form, or MOP changes and provide updates on Steering Committee decisions.

3.C.4.b Membership

The Coordinator Committee consists of the DCC team (Scientific Coordinator and Data Management representatives) and at least one coordinator from each CRC site.

Chair: (DCC)
DCC:
DCC:
Lead Coordinators:
Kaiser:
Vanderbilt:
Yale – Cincinnati:
Yale – Montreal:
Yale – New Haven:
Yale – London/Ontario:
University of Washington:

3.C.4.c Responsibilities

The Coordinator Committee identifies any protocol, forms, and/or MOP issues at the site level. Unresolved issues will be brought to the attention of the QCC.

3.D Biomarker Partners Committee (BPC)

3.D.1 Purpose

The BPC identifies partners in the scientific and industrial community who will assist with biomarker measurement on the samples collected by the ASSESS-AKI study.

3.D.2 Membership

The NIDDK Project Scientist, DCC PI, an investigator from each CRC, representative of the DCC, and at least one coordinator comprise the BPC.

Chair:
NIDDK:
DCC:
Kaiser:
Vanderbilt:
Yale:
University of Washington:

3.D.3 Responsibilities

Responsibilities of the BPC include identification of core list of biomarkers that will be measured and the quantities needed, identification of potential biomarkers, reviewing the RFPs from central lab applicants and biomarker partners, and reviewing any ancillary study proposal that requests biospecimens. In addition, the BPC establishes protocols for data/sample flow in the study.

3.E Ancillary Studies Committee (ASC)

3.E.1 Purpose

The Ancillary Studies Committee (ASC) and the Steering Committee (SC) must review and approve all proposed ancillary studies before their inception or submission of proposals for external funding consideration.

An ancillary study is defined as any new project proposal based on information derived from ASSESS-AKI Study participants in an investigation or analysis that is relevant to, yet not described in, the ASSESS-AKI Study protocol, and that derives support from non-ASSESS-AKI core or supplement funds. An ancillary study may propose the collection of additional data not collected or analyzed as part of the routine ASSESS-AKI Study data set. Ancillary studies may be submitted by the investigators within the Consortium or by investigators without a prior relationship to the Consortium. However, any non-ASSESS-AKI investigators would need to collaborate with an ASSESS-AKI Consortium investigator to submit an ancillary study proposal. Ancillary studies require external (non-ASSESS-AKI) funding to cover all associated costs.

3.E.2 Membership

The Ancillary Studies Committee (ASC) is chaired by the Chair of the ASSESS-AKI Steering Committee.

Chair:
NIDDK (ex officio):
DCC:
Kaiser:
Vanderbilt:
Yale:
Washington:

3.E.3 Responsibilities

The major responsibilities of the ASC are to review all proposed ancillary studies and to assess the merit of each proposed study, advantages and disadvantages with respect to ASSESS-AKI goals, burden of the proposed measurement collection on the ASSESS-AKI study, sites, and participants, and suitability for endorsement by the ASSESS-AKI SC.

ASC develops policies relating to the distribution of data and biological specimens generated by ASSESS-AKI to non-ASSESS-AKI investigators. Those policies are approved by the voting members of the SC. The ASC evaluates and makes recommendations for use of data or biologicals by specific outside (i.e. non-ASSESS-AKI) investigators. Decisions in this regard are to be recommended to the SC for final decision by voting members.

All policies and recommendations need to be in accordance with NIH and federal guidelines, and when possible in accordance with individual institutional guidelines. Policies and recommendations (internal and external) will be dictated by the nature of the informed consents signed by the participants.

3.E.4 Guidelines for Recusal

There are no guidelines for recusal. If someone feels that s/he cannot speak freely about a study, the person would contact the Chair of the ASC with a request for recusal. The SC Chair may also request specific committee members be recused if a significant conflict of interest exists for that member.

3.F Event Adjudication Committee

3.F.1 Purpose

The Event Adjudication Committee centrally adjudicates potential outcome events based on review of relevant medical records.

3.F.2 Membership

Cincinnati Reviewers:

Ontario Reviewers:

New Haven Reviewers:

Montreal Reviewers:

University of Washington Reviewers:

Kaiser Reviewers:

Vanderbilt Reviewers:

The Event Adjudication Committee is chaired by one of the Principal Investigators and is comprised of three physician investigators from each of the CRCs as reviewers.

3.F.3 Responsibilities

Two Committee members (reviewers) will review a potential clinical event that is assigned by the DCC and follow standardized criteria consistent with the approach being used in other prospective renal cohort studies (e.g., CRIC).[91]

The two reviewers will be from a different site than the one where the event occurred. Reviewers will have two weeks to submit a final review. The reviewer will decide if it is definitely an event, probably an event, possibly an event, not an event, or other. The "other" option will be used if the reviewer finds a new event other than the event being reviewed and which was not identified. If another event is found, the DCC notifies the site and the process begins. If no review is received by the DCC, an email reminder will be generated. If both reviewers do not agree, a teleconference will be held to reach a consensus and if needed, a specialist will make the decision. Refer to the Event Adjudication MOP for additional details.

3.G Publications and Presentations Committee (Pub-Pres C)

3.G.1 Purpose

The purpose of the Publications and Presentation Committee (Pub-Pres C) is to ensure timely completion of manuscripts and presentations, equitable access to authorship, and adherence to the ASSESS-AKI

Study Publication and Presentation Policy.

3.G.2 Membership

3.G.2.a Membership

Chair:
NIDDK:
DCC:
Kaiser:
Vanderbilt:
Yale:
Washington:

3.G.2.b Structure of the Publications Committee

The Publications and Presentation Committee (Pub-Pres C) will be composed of six (6) voting members: the PIs of the four (4) ASSESS-AKI Clinical Centers or their designees, the PI of the DCC or his designee, and one (1) representative from the NIDDK.

The Data Coordinating Center (DCC) will assume primary responsibility for preparing presentations and publications. DCC will provide editorial and clerical assistance with publications. DCC will direct the administrative aspects of abstract and manuscript submissions for societal conferences and journals that include gathering and reporting COI, acknowledgement, proofreading, distribution, and reprints. As needed, the DCC will assist with production of reference lists and formal presentations.

3.G.2.c Formation of Writing Committees

a. The Pub-Pres C will provide oversight in the process of convening Writing Committees and defining lead (first and last) authors.
    - In most cases, it is expected that the individual proposing a Core Manuscript will serve as 1st author or senior author. In either case, the name of the proposed 1st author or senior author name and rationale will be submitted to the Pub-Pres C at the time of proposal submission. A corresponding author will be proposed, along with a rationale, at the time of proposal submission.
    - The Pub-Pres C will decide on the 1st, senior and corresponding author at the time of its initial review. In certain circumstances, deliberations with the Steering Committee (SC) might be necessary and will be initiated on a case by case basis. In case of disagreement, the SC will make the final decision. Proposed changes to approved 1st author or corresponding author designations must be approved by the Pub-Pres C.
    - For an approved manuscript pertaining to the primary specific aims of an ASSESS-AKI Ancillary Study, the principal investigator of that study will likely serve as the 1st or senior author. Item 3.G.2.b. is also applicable in this case.
    - The priority for other authors is defined in this document. However, the Pub-Pres C need not strictly adhere to this guideline when there is an acceptable rationale and this would be decided on a case-by-case basis. To assist in selection of Writing Committee members when

more candidates are identified than can be accommodated, a priority ranking can be used as follows: first – ASSESS-AKI PIs, second – ASSESS-AKI Core Investigators, and third – ASSESS-AKI Team Members. This priority ranking is meant to be a general guideline.

b. Principles for formation of Writing Committees for both types of ASSESS-AKI manuscripts.

- Ordinarily, the individual proposing a Core Manuscript or the principal investigator of an ASSESS-AKI ancillary study will serve as the Writing Committee Chair for the manuscripts
- The Pub-Pres C will select the Writing Committee Chairs based on expertise, available time, and commitment.
- The selection of trainees with K23 or similar awards will take special consideration.
- The Pub-Pres C will generally request an indication of interest in joining a Writing Committee from PIs, core investigators team members and relevant ancillary study investigators, if relevant.
- The Pub-Pres C will prioritize membership in the Writing Committee if necessary.

c. Principles to be used by the Pub-Pres Committee to guide achievement of adequate representation of ASSESS-AKI core and ancillary investigators in writing groups:

- For ASSESS-AKI Study papers not directly addressing a specific aim from an ancillary study, representation, if possible, of all five (5) ASSESS-AKI entities with voting rights at which individuals from these entities indicate an interest and commitment.
- For ASSESS-AKI Study papers directly addressing a specific aim from an ancillary study, representation, if possible, of all clinical sites involved in data collection for that particular ancillary study, the NIH, and the DCC, at which individuals indicate an interest and commitment.

d. Changes in Scope of Approved Manuscripts.

- The Pub-Pres C will monitor the activity of Writing Committees to decide 1) whether a major change in the previously approved specific aims for a previously approved manuscript is justified, 2) whether more than one manuscript should be created on a topic previously approved as a single manuscript, and 3) if withdrawal of plans to complete an approved manuscript is justified.

e. Writing Committee Responsibilities.

- The Writing Committee is responsible for all phases of manuscript preparation including (but not limited to):
- Preparation of the manuscript proposal, the identification of data elements and statistical analyses needed, and assignment of tasks to Writing Committee members, preparation and circulation of drafts, determination of the order of authorship on the manuscript, and submission for publication. All members of Writing Committees will be required to participate in Writing Committee activities and be able to confirm that they:
  - gave final approval of the submitted manuscript.
  - participated sufficiently in the work to take public responsibility for its content.

- made substantial contributions to the intellectual content of the paper through:
  - conception and design of the work, OR acquisition of data, OR analysis and interpretation of data,

    AND

  - drafting OR critical revision of the manuscript for important intellectual content,

    AND

  - statistical analysis, OR obtaining funding, OR administrative or technical support, OR supervision.

3.G.3 Responsibilities

Major responsibilities of the Pub-Pres C are to develop a process for commissioning and review of all manuscripts and scientific abstracts from ASSESS-AKI studies that are undertaken and to monitor the development and progress of these manuscripts as well as to arbitrate disputes. All policies require approval of the full SC prior to implementation.

3.G.4 Guidelines for Recusal

There are no guidelines for recusal. If someone feels that s/he cannot speak freely about a presentation or publication, the person would contact the Chair of the Pub-Pres C with a request for recusal. The SC Chair may also request specific committee members be recused if a significant conflict of interest exists for that member.

4 NIDDK-APPOINTED COMMITTEES

4.A External Expert Panel (EEP)

4.A.1 Purpose

The NIDDK has formed an EEP, formerly named the External Expert Group (EEG) and External Advisory Group (EAG). The EEP functions in an advisory capacity to the Director of the Division of Kidney, Urologic and Hematologic Diseases of the NIDDK.

4.A.2 Membership

The EEP is selected by the NIDDK. The EEP includes individuals with expertise in nephrology, AKI, cardiovascular disease, biomarker biology, biostatistics, and bioethics and consumer advocacy as necessary. No EEP member is associated with the institutions represented by the DCC and the CRCs.

4.A.3 Responsibilities

The EEP may propose modifications to the ASSESS-AKI study and monitors study progress and patient safety issues. One of the functions of the EEP is to review the objectives, hypotheses, design, and analytic plans developed by the ASSESS-AKI. The EEP will not participate in the conduct of research or publication of results of the work performed by the SC or CRCs.

The DCC, along with selected CRC investigators, will present the protocol and results of analyses to the EEP. The EEP will review study performance and quality of the study data. NIDDK staff will serve as the Secretary of the EEP. Summary reports of the EEP meetings prepared by NIDDK staff will be distributed to each Consortium PI by the DCC within 30 days following each EEP meeting. These summary reports include a statement that an EEP review of the data and outcomes across all CRCs took place on a given date, and the EEP's summary comments with respect to study progress and/or potential suggested protocol modifications. The DCC will forward these summary reports to its IRB, and the Consortium PIs will be required to forward them to their local IRBs. The EEP will evaluate the protocol's integrity, protection of patients' study rights, and potential risks.

5 STANDING POLICIES AND PROCEDURES

5.A Protocol Development and Implementation

5.A.1 Protocol Concept Development

A preliminary concept for a study is formulated in writing by a SC member (although the idea can come from any source) and presented to the SC. Concepts submitted from outside the SC can be presented by a PI or the NIDDK Project Scientist. If the concept is approved by the full SC, it becomes the responsibility of the SC Chair to select a member of the SC to develop a detailed "preliminary protocol" (4-5 pages) for clearance by the SC. The preliminary protocol should include rationale and importance of the study, estimates of subjects needed, recruitment rates required, project length, endpoints, staff time, and resource estimates to perform the study.

5.A.2 Preparation, Review and Approval

A majority of the SC must approve a "preliminary protocol" before it is considered for implementation. Once approved by the full SC, a complete draft protocol will be prepared by the appointed SC member. Once the draft protocol is final, the DCC assumes the responsibility for the finalization and dissemination of the protocol.

5.A.3 Authorization to Implement the Protocol

Once the protocol is approved by the SC, the DCC prepares data collection forms and a Manual of Operations for the specific study in collaboration with the appointed SC member. A project timeline is developed from start of recruitment through data analysis and publication. The final protocol, with an appended estimate of implementation parameters, is reviewed by the EEP and NIDDK, which provides final authorization to implement the protocol.

5.A.4 Planning Implementation of the Protocol

The SC plans the protocol start-up. All CRCs must be certified as having met any special requirements for participation in the study: Coordinator training, computer readiness, IRB approval, etc.

5.A.5 Protocol Implementation

The SC monitors protocol implementation. The QCC is responsible for assuring quality control for each study protocol. This committee is also responsible for making recommendations for site visits when problems are identified, with ad hoc reviewers as indicated.

5.A.6 Protocol Revisions to the Primary Study

All proposed edits are brought to the attention of the PI of the study and the PI of the DCC. They will decide if the change is minor or major. Minor edits are presented to the QCC and then subsequently to SC for approval. Once the changes have been approved, the DCC will be responsible for editing the protocol and making the revised copy available to the CRCs.

A major change is one that affects the design of the study or results in a substantial change in eligibility criteria or measurement of primary outcome variables. Major edits are presented first to the SC for approval. Once approved, the DCC will inform the EEP of the proposed change. If there are concerns, a telephone conference will be set up with the EEP. The PI for the study (or QCC), PI of the DCC, Chair of the SC, and NIH Project Scientist may participate in this conference as needed.

If the revisions are substantive, it will be the responsibility of the individual CRCs to obtain IRB approval. Once the changes have been approved, the DCC will be responsible for editing the protocol and making the revised copy available to the CRCs.

5.B Informed Consent

The CRCs are responsible for recruiting participants and obtaining informed or surrogate consents. The DCC is responsible for assuring that each local IRB has approved the protocol for a Consortium study and

the procedures for recruitment, and has reviewed and approved the informed consent document. A Consortium study cannot begin at a CRC until that CRC has submitted IRB approval(s) to the DCC. Informed and surrogate consent documents and signatures are retained at the CRCs. The CRCs will recruit participants by adhering to HIPAA regulations from "standing" populations at the CRCs by research, pharmacy, and disease management databases, by referral from collaborating physicians, and by advertisement (flyers, brochures, posters, news media, etc). The DCC will provide real-time accrual reports for each CRC at the password-protected Consortium web site, listing the enrolled participants and any reasons for exclusion between the inpatient and outpatient periods. This routine monitoring allows for early identification and resolution of potential problems during the recruitment phase. The recruitment duration will be specified for each study.

The DCC develops a template for the informed/surrogate consent documents for each protocol, including the mandatory language referencing the NIDDK Repository. The goal of the consent process is to establish and maintain procedures aimed at providing each potential participant with sufficient time and information to make informed decisions about participation in a Consortium study. The cornerstone for research on human beings is voluntary consent based on accurate information. The consent process is one of the more important participant-investigator activities because, if done properly, it serves not only to inform but also to establish and enhance relationships between the participant and the CRC staff. Moreover, the consent process that is employed in the Consortium is a continual process with continued education of participants about the study. Amendments to consent and re-consenting may be needed as additional important information becomes known to the Consortium. HIPAA authorization language will be included, as necessary, in the confidentiality section of the informed consent form.

5.C Required Education in the Protection of Human Subject Research Participants

On October 1, 2000, the NIH implemented a policy that requires education on the protection of human research participants for all investigators submitting NIH applications for grants or proposals for contracts or receiving new or non-competing awards for research involving human subjects.

Protections for human subjects of research are required under Department of Health and Human Services (HHS) regulations at 45 CFR 46. Subpart A of the HHS regulations constitutes the Federal Policy (Common Rule) for the Protection of Human Subjects.

5.D Confidentiality of Subject Information

Extensive procedures are in place to protect participant confidentiality, including transmission of all study data without linkage to personal identifiers. If participant confidentiality is compromised, the DCC treats it as a high-level protocol violation and informs the NIH, the EEP, the QCC, and the CRC responsible for the transgression.

All medical interactions, data collection, and treatments will be maintained with confidentiality and professionalism. No information ever will be released that could identify an individual participant. Procedures will be implemented in each Consortium protocol for the protection of human subjects: creation of understandable consent documents; adherence to a formal consent process; linkage of a participant's protected health information by a study ID number and only those HIPAA identifiers necessary to perform appropriate analyses; and procedures for identifying, reporting, and reviewing adverse events. Any

participant who withdraws consent to participate, or for whom the study physician determines that continuation in the study would not be in the best interest of the participant, will be assigned withdrawal status.

5.E Source Documentation

5.E.1 Primary Goal of Source Documentation Policy

The objective for setting an ASSESS-AKI Consortium source document policy is to provide the CRCs with a mechanism by which to substantiate participant data.

5.E.2 Definition of a Source Document

A source document is an original source or document that permits the verification of the existence of a study participant and substantiates the integrity of the data collected during a clinical trial. Common source documents include medical records, clinical progress notes, original informed consent forms, laboratory notes, ECG tracings, research study pre-screening forms, correspondence, and appointment books. In fact for many data fields, the original case report form will be the source document.

5.E.3 ASSESS-AKI Consortium Source Document Requirements

Some specific source documents will be required. Others will be optional. The availability of certain source documents will differ between CRCs due to varying institutional requirements and practices for study documentation. For instance, the paper medical record, which constitutes a significant source document, is not available at some CRCs.

Examples of required source documents are: informed consents, clinic appointment book, participant assignment logs, and ECG tracings.

5.E.4 Source Documentation Responsibilities

The responsibility for source documentation is shared by the DCC, the Research Coordinator, and the CRC PI. To begin, the DCC is responsible for communicating the specific source document policy to the Research Coordinators. The CRC PI and Research Coordinator are charged with maintaining adequate source documentation and with ensuring that all original source documents are available during any ASSESS-AKI site visits for data verification and audit purposes. Finally, the DCC closes the source documentation loop by conducting the source document verification review and data quality audit during the site visits to each CRC.

5.F Exception, Protocol Excursion, Protocol Violations, and Rebuttal Process

Three classes of departures from ASSESS-AKI procedure or protocol are designated for identification, tracking, and reporting. These include protocol exceptions, protocol excursions, and protocol violations as defined below.

5.F.1 Protocol Exceptions

Occasionally a CRC will screen a participant or enroll a participant and find that he or she meets all but one of the eligibility criteria (e.g., the participant was hospitalized for 91 days and there were extenuating circumstances). In such cases, the Research Coordinator may contact the Scientific Coordinator at the DCC for a protocol exception. Depending on the nature of the request, the Scientific Coordinator may consult with the DCC PI and/or the Quality Control Committee before a final decision is reached and communicated to the center. Exceptions that are requested and granted by the DCC before any action is taken by the center are tracked in an "Approved Exceptions" table, distinct from protocol violations and protocol excursions.

If an adult participant is anuric (i.e., unable to produce the 3mL of urine during the inpatient stay) due to AKI, the participant will not be excluded from the study. The site coordinator should contact the DCC Scientific Coordinator for an exception.

Before conducting an in-center visit as a phone interview or passive chart abstraction, request a protocol exception. Refer to the Protocol-Specific MOP, Passive Chart Abstraction.

In reference to protocol exceptions requested for visit 3M window extensions to avoid a mistimed procedure, sites should request these prior to performing the interview or biomarker collection. Sites should adjust interview times within the preferred windows (See Protocol-Specific MOP, Appointments) as much as possible to maintain these time points. Visits that occur before or after the visit window, except with Visit 3M, and any skipped visits need to be documented by the CRC. A spreadsheet is posted on the ASSESS website for each CRC to document these occurrences.

If a CRC fails to request an appropriate exception and instead proceeds with participant enrollment on its own judgment, a protocol violation or protocol excursion will be assigned as follows. If the DCC identifies a problem with participant eligibility criteria when the data are submitted, and no documentation of an approved exception exists, the issue will be referred to the Scientific Coordinator for review. If the exception ultimately is allowed, then necessary data corrections will be made to the database and the failure of the center to obtain prior approval will be tracked as a protocol excursion. If the exception is not allowed, the participant will be considered ineligible and a protocol violation will be assigned. Participants who have already been enrolled may be allowed to continue at the discretion of the DCC PI and the Chair of the Quality Control Committee.

In reference to protocol exceptions requested for Visit 3M window extensions to avoid a mistimed procedure, sites should request these prior to performing the interview or biomarker collection. Sites should adjust interview times within the preferred windows (See Protocol-Specific MOP, Appointments) as much as possible to maintain these time points. Visits that occur before or after the visit window, except with Visit 3M, and any skipped visits need to be documented by the CRC. A spreadsheet is posted on the ASSESS website for each CRC to document these occurrences.
The Visit Exceptions spreadsheets can be found on the ASSESS website, and the coordinator has access only to its site's spreadsheet. Refer to the Document Management MOP, Section 2 for more information on how to fill out the spreadsheet. There are also instructions in the Visit Window Exceptions folder under "How to Document Protocol Exceptions" and "How to Edit and Repost Visit Window Spreadsheet."

5.F.2 Protocol Excursions

Protocol Excursions are defined as departures from a study protocol or ASSESS-AKI methods of procedure that do not pose a risk to subject safety, and do not adversely affect data quality or the integrity of the major scientific goals of the study, AND do not involve a significant and repeated breach of subject privacy. Protocol excursions include (but are not limited to):

- failure to obtain appropriate source documentation
- failure to achieve appropriate ASSESS-AKI certification prior to performing procedures
- mistimed procedures (performing a lab test or visit outside the window outlined in the protocol)
- using an outdated version of a data collection form

If certification-related excursions persist at a given center and an uncertified individual continues to carry out study procedures without proper ASSESS-AKI training, serious effects on data quality may result. Such a scenario leads to the possibility of protocol violations being assigned. Likewise, if an outdated version of a form used by a center in error references incorrect study eligibility criteria, protocol violations may be assigned. These situations will be reviewed and classified on a case-by-case basis by the protocol's Scientific Coordinator, a member of the DCC, in consultation with the DCC PI and the Quality Control Committee.

If a given center allows identifying information to be sent to the DCC, lab, reading center, or any other ASSESS-AKI-affiliated group on more than one occasion, this repeated breach of privacy will be tracked as a protocol violation, in addition to the individual protocol excursions. Each time two new protocol excursions accrue in the category of "blinding of identity," a new protocol violation will be assigned in this category.

If a given center experiences a high frequency of protocol excursions in a specific area, the DCC will address this issue with the PIs of the center and the NIDDK in an effort to resolve the problem.

5.F.3 Protocol Violations

Protocol violations are defined as departures from accepted research practices, study protocol, and/or ASSESS-AKI methods of procedure that pose a risk to subject safety, adversely affect data quality, significantly affect the integrity of the major scientific goals of the study, and/or involve a significant and repeated breach of subjects' privacy. Protocol violations include (but are not limited to):

- failure to obtain informed consent appropriately
- enrollment of ineligible subjects
- omission of protocol and/or ASSESS-AKI procedure elements
- failure to carry out study procedures in the appropriate order, when applicable
- misplacement/loss of biological specimens
- misplacement/loss of study documentation or data/ data collection forms

- submission of subject identifying information (e.g., name, address, phone numbers) to the DCC, or other groups dealing with subject specific ASSESS-AKI data

By the nature of their definition, protocol violations are considered the most serious class of departure from the study protocol. All protocol violations will be reported to the center PI, the DCC Principal Investigator, the NIDDK, and the Quality Control Committee.

5.F.4 Protocol Violation Rebuttal Process

Occasionally a protocol violation may be assigned with which the center does not concur. In this situation, the Research Coordinator may submit a formal rebuttal of the violation to the DCC for consideration and resolution. Rebuttals must meet the following criteria, and they must be submitted within 42 days of the assignment of the protocol violation on the center's report.

Rebuttal Criteria:

a. The rebuttal must take the form of a formal memo written by the Research Coordinator. The memo should be addressed to the Scientific Coordinator at the DCC.

b. The rebuttal must clearly state the violation code, the subject ID number, visit number and date assigned from the Protocol Violation Report.

c. The rebuttal must include a concise statement of the Research Coordinator's view of the situation, along with any additional details that support the revocation of the violation. If appropriate, supporting documents should be attached to the memo.

d. The rebuttal must be signed by the Research Coordinator and the site PI, addressed to the Scientific Coordinator, and mailed to the DCC.

5.F.4.a Rebuttal Review Process

Once the rebuttal document has been received at the DCC, the Scientific Coordinator is responsible for reviewing the memo, the Protocol Violation Report, and the submitted information. If the DCC Scientific Coordinator does not believe the violation should be revoked on the basis of submitted evidence, then he or she will forward the rebuttal and other documentation to the DCC PI and Chair of the Quality Control Committee for review, along with his or her comments. The QCC will make the final decision; the QCC representative from that site should not participate in the review and decision.

In all cases, the DCC Scientific Coordinator will send a formal written reply to the Research Coordinator who initiated the process stating the decision that was reached. If the decision is to revoke the violation, then the updated Protocol Violations report will reflect this change. The Scientific Coordinator will provide copies of the rebuttal and resolution memos (and supporting documents) to the protocol Data Manager at the DCC for filing.

In general, this rebuttal process applies only to protocol violations and not to most protocol excursions. In the case of certification protocol excursion, if a supervisor ID is inadvertently omitted from a form that an uncertified individual completed, a protocol excursion will be logged. It is suggested that Research

Coordinators carefully review the forms in visit packets for certification requirements prior to data entry so that related issues can be resolved before protocol excursions are assigned.

In cases where the Research Coordinator identifies an error in protocol excursion assignment, no formal rebuttal is necessary. The Research Coordinator should contact the DCC Scientific Coordinator directly to have the error corrected. Errors in tracking the dates of interviewer certification in various procedures can result in the assignment of erroneous protocol excursions. These are easily verified and corrected by contacting the DCC.

5.G Data Access

5.G.1 Data, Reports, and Analyses During the Study

During and after a study, reports and analyses will be generated by the DCC in response to requests from the SC, EEP, or NIDDK. Prior to a meeting of the SC or EEP, the SC will determine reports to be presented at the meeting. Their requests will be conveyed to the PI at the DCC, who will then oversee the preparation of the reports. For EEP meetings, all reports will be presented only to members of that committee and will be treated with the strictest confidentiality, including collecting all copies of the reports at the end of the EEP meeting.

Routine reports of descriptive data (e.g., descriptive statistics of baseline data) may be presented to the SC as requested during the study. Statistical analyses of study results will be performed under the direction of the SC.

5.G.2 Database Availability After the Study

While the study is underway and primary publications are being developed, access to the database will be restricted to certain personnel at the DCC and the NIDDK. Within a period of time to be determined after publication of the primary results, a documented copy of the final study database will be made available to all CRCs. Awardees will retain custody of and have primary rights to the data developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies. The collaborative protocol and governance policies will call for the continued submission of data centrally to the coordinating center for a collaborative database; the submittal of copies of the collaborative data sets to each PI upon completion of the study; procedures for data analysis, reporting and publication; and procedures to protect and ensure the privacy of medical and genetic data and records of individuals.

The NIDDK Project Scientist, on behalf of the NIDDK, will also have the same access, privileges, and responsibilities regarding the collaborative data as the other members of the SC. Awardees are encouraged to publish and to publicly release and disseminate results, data and other products of the study, concordant with the study protocol and governance and the approved plan for making data and materials available to the scientific community and the NIDDK. However, during or within the period beyond the end date of the project period of NIDDK support, unpublished data or products are to be made available to any third party only with the approval of the SC. Upon completion of the project, the DCC is expected to put all study intervention materials and procedure manuals into the public domain and/or make them available to other investigators, according to the approved plan for making data and materials available to

the scientific community and the NIDDK, for the conduct of research at no charge other than the costs of reproduction and distribution.

Twelve months after funding has ended for the study, data and samples will be transferred to the NIDDK Repository and the responsibility for distribution will rest with the NIDDK.

5.H Biomarker Studies Policy

1. All proposed ASSESS AKI biomarker studies, must be submitted in written protocol format in time for circulation to the Biomarker Partners Committee (BPC) and must receive a favorable review from a majority of voting members of the Steering Committee (SC).
2. All costs for conducting the biomarker study must be included in the final proposal before it goes to the SC. Such costs might include sample collection and aliquoting, shipping, assays/reagents, data analysis, and others as necessary.

5.H.1. Request for a Biomarker Study

A written request for approval of a biomarker study should be submitted to the Biomarker Partners Committee (BPC) as a two- to three-page summary containing the following information:

1. Project Identifiers
    a. Project title
    b. Biomarker(s)
    c. Population
    d. Time points
    e. Complete or partial cohort
    f. Identification of BPC investigator to oversee the project
    g. Collaborators
    h. Planned starting date and project timeline
    i. Funding source (Core, supplement)
        i. If a supplement, identify the funds number
    j. Estimated cost
    k. Where will the data analyses be conducted?
2. Sample Requirements and Selection
    a. Specify type
    b. Specify minimum amount.
    c. Changes to biological sample tracking (BST), sample flow, and/or label template.
    d. Where are the samples that will be used?
    e. How many participants are required?

f. How will participants be selected?

g. What, if any, will be the target ratio of AKI to non-AKI subjects?

h. Will duplicates be needed?

i. If yes, how/who will select the duplicates?

3. Contract questions

a. What lab will be used?

b. Is a sole-source justification (SSJ) needed (>$10,000)

c. Will this be an amendment to a contract?

d. What is the PO #?

e. When and in what form will a complete data set be returned to the ASSESS AKI Study?

5.I Ancillary Studies Policy

1. Before submission to a funding agency, all proposed ancillary study applications must be submitted in written protocol format in time for circulation to the Ancillary Studies Committee (ACS) and must receive a favorable review from a majority of voting members of the SC. Studies submitted for review less than twelve (12) weeks before a funding application deadline may not receive approval. The proposal is submitted to the Chair of the ASC and to the DCC. The ASC Chair calls a meeting of the ASC. The ASC reviews the proposal, votes, and makes a recommendation to the ASSESS AKI Biomarker Partners and Steering Committees. The Biomarker Partners Committee must approve the proposal before it goes to the Steering Committee. The ASSESS AKI Steering Committee members email their votes to the PI of the DCC. The DCC notifies the investigator if the proposal has been approved or not.

2. At least one ASSESS-AKI PI must be included in an ancillary study. The ASSESS AKI Steering Committee strongly encourages the close collaboration of all PIs in ancillary studies.

3. All costs for conducting the ancillary study must be included in the final proposal. Such costs might include sample collection and handling, data collection, data analysis, obtaining additional consent from participants, and others as necessary.

4. Data collected by the ancillary study on ASSESS AKI participants will be transferred to and stored by the ASSESS AKI DCC. The ASSESS AKI DCC will conduct analyses of ancillary studies unless different arrangements are made before the ancillary study begins.

5. Funding for ancillary studies may be from an educational institution, private foundation, the NIH, or other sources. Investigators planning to submit an application to the NIH should have discussions with the NIDDK Project Specialist for ASSESS AKI. Applications for NIH grant support will be revised through the traditional peer review mechanism and compete for available resources with research project grants.

6. The policies regarding publications and presentations of the result of the ancillary studies are the same as those governing the publications and presentations of results of the main study. These policies are designed to:

a. Assure timely publication of the results to the appropriate professional audiences.

b. Avoid premature publications of results that might compromise the performance of the main study or that might compromise the ability to publish the results in high quality peer reviewed journals.

c. Maintain high standards of published material.

d. Guard against duplicate publication of results.

e. Assure equitable attribution of credit to all of the professionals participating in the ancillary study and the main study.

5.I.1 Request for an Ancillary Study

A written request for approval of an ancillary study should be submitted to the ASC as a two- to three-page summary containing the following information:

1. Project Identifiers
    a. Project title
    b. Initiating investigators, collaborators, at least one ASSESS-AKI Study co-investigator
    c. Identification of ASSESS AKI investigators to be involved in the project (see policy above)
    d. Planned starting date and project timeline
    e. Funding plans and estimated cost
2. Design and Methods
    a. Brief background and rationale
    b. Specific study questions and hypotheses
    c. Specific data collection methodology, including questionnaires and coding forms, if available.
3. Specific Answers to the Following Questions:
    a. What is the expected burden to participants? What are the specific time burdens, discomfort, and expected participation rates?
    b. What ASSESS-AKI Study core data and/or analyses are needed for the ancillary study? Will the current participant visit/contact structure be used or will there be additional forms, form changes, or other proposed participant measures?
    c. Is blood or other biologic samples (either fresh or from the ASSESS-AKI Study's repository of stored samples) required? What will be the quantity of specimens needed? What time points are these samples proposed to be collected?
    d. What collaboration with ASSESS-AKI Study investigators is planned? With whom? Have the collaborating investigators approved the proposal?
    e. What, if any, follow-up is needed? Specify length of time and events to be ascertained.
    f. How many participants are required? How will participants be selected? What, if any, will be the target ratio of AKI to non-AKI subjects?

g. When will data be collected? Could the ancillary study be deferred to a later exam cycle?

h. How will the ancillary study be funded? Would any additional un-reimbursed work or personnel time be expected of the ASSESS-AKI Study? How will the ancillary study budget cover demands on ASSESS-AKI Study personnel time and resources?

i. Where will the data analyses be conducted?

j. How will the confidentiality and other aspects of protection of human subjects be maintained?

k. When and in what form will a complete data set be returned to the ASSESS-AKI Study?

4. Data or Specimen Requirements
   a. Data needed from ASSESS-AKI Study analysis files
   b. Specimens needed from ASSESS-AKI Study repositories, specifying type, amount, and time point.
   c. Changes to biological sample tracking (BST), sample flow, and/or label template.
5. Handling of ASSESS-AKI Study Data and Specimens
   a. Disposition of stored samples from main study and those processed by ancillary study
   b. Disposition of ancillary study data at the conclusion of the ancillary stud

5.I.2 Evaluation of Proposed Ancillary Study

The criteria by which the Ancillary Study will be evaluated by the ASC and SC are:

1. Threats to integrity of main study
2. Participant burden
3. Resources needed – biosamples, DCC effort, site investigators' effort
4. Burden to DCC or sites
5. Relevance to Parent study objectives
6. Feasibility of proposed study
7. Funding plans – adequacy and overlap
8. Scientific overlap with existing or proposed studies
9. Overall scientific priority

The SC chair will inform the PI of the proposed Ancillary Study the decision of the SC. In the event of a negative decision, the Ancillary Study PI may appeal to the SC (in writing) once. No further appeals will be accepted.

5.I.3 Procedures for Ancillary Studies after Steering Committee Approval

1. Authors of the approved Ancillary Study are required to inform the Steering Committee of the expected date of submission and expected date of review.

2. Ancillary Study authors are required to inform the SC of the outcome of the review and the planned response to the review within 30 days of the receipt of the reviews. If the SC does not receive any information within this time the Ancillary Study proposal will be considered inactive.
3. Once an ancillary study proposal is funded, all changes in the structure or concept of the study proposal shall be disclosed to the Ancillary Studies Committee and to the ASSESS-AKI SC for review and approval.
4. Approved and funded Ancillary Studies shall make periodic reports to the ASSESS AKI Steering Committee regarding the progress of the study. The ASSESS AKI Steering Committee may make requests for additional information regarding quality control, enrollment, data processing, or other matters related to the conduct of the study.
5. The SC will report Ancillary Studies activities to the External Expert Panel (formerly EAC) at their periodic meetings.

5.J Private Sector Collaboration

5.J.1 Participating Laboratories

Participating laboratories will consist of a central laboratory (University of Minnesota) for measurement of core clinical parameters and novel biomarkers and all the local laboratories at the clinical sites (Kaiser Permanente of Northern California, Vanderbilt University, Yale University, London Health Sciences Center [Ontario], University of Washington, University of Cincinnati Children's Hospital, and Montreal Children's Hospital).

Systematic information on specific assay details will be obtained for all locally performed tests to ensure comparability of accuracy and reproducibility of results across CRCs, which will all use different local laboratories.

5.J.2 ECG Reading Center

The ASSESS-AKI Central ECG Reading Center (EPICARE, Wake Forest) reviews all ECGs obtained through the study visits and as needed, to facilitate event adjudication for acute coronary syndromes.

Before January 30, 2013 we obtained 12-lead surface electrocardiograms of the adult participants at the baseline study visit and every subsequent in-person, in-clinic study visit, not at the home visits or of any pediatric participant. After January 30, 2013, ECGs were obtained from the Kaiser and the University of Washington sites.

After October 2, 2014, the following applies to all adult sites.

For adult participants, we will obtain 12-lead electrocardiograms at the in-clinic three-month study visit and every subsequent in-clinic study visit. Acceptable ECGs include those done by research personnel and those done in clinical ECG laboratories or available through clinical paper or electronic medical records.

- V0/V3M – all adult sites should make every effort to get an ECG either through their research center protocol (most preferred) or retrieved from their clinical ECG department and/or medical records. For participants who have already completed the V3M visit but in whom research personnel did not obtain an ECG at that time, clinical records from the site should be reviewed and a clinical ECG most proximate and preceding the V3M visit should be obtained. This ECG could be obtained at an outpatient visit or during hospitalization. It is recognized that for some participants,

this ECG may have been obtained during the V0 hospitalization. Preferably, an ECG nearest to the hospital discharge date would be available and would be acceptable.

- In-center visits – all adult sites should obtain an ASSESS-AKI ECG for all visits (either through their research center or send the participant to the ECG lab), or retrieve a clinically-obtained ECG from the medical records within the follow-up window.
- Home visits/Phone visits in lieu of in-center visits – all adult sites should attempt to obtain mobile ECG or if not possible, they should retrieve a clinical ECG from medical records within the follow-up window or if not available, nearest to the follow-up window.

The ASSESS-AKI Central ECG Reading Center, Wake Forest, electronically receives digital electrocardiograms and provides a systematic evaluation for relevant electrocardiographic findings.

5.J.3 Equipment

5.J.3.a Equipment Specifics

Site	Height	Weight	BP
Kaiser	Perspective Enterprises Model No. PE-WM-60-84	UC-321 PL High Capacity Telemedicine Scale	Omron 907 for adults
Vanderbilt	UC-321 PL High Capacity Telemedicine Scale		Omron HEM-907XL
Yale	SECA 217 Road Rod portable stadiometer	UC-321 PL High Capacity Telemedicine Scale	HEM705CPN
London	SECA 217 Road Rod portable stadiometer	UC-321 PL High Capacity Telemedicine Scale	HEM705CPN
Washington	Healthometer – home visits SECA 213 and Scaletronix– clinic visits		Omron BP 785 – home visits Omron HEM-907XL
Montreal (peds)	SECA 217 Road Rod portable stadiometer*	UC-321 PL High Capacity Telemedicine Scale TANITA Model 1583	Dinamap ProCare 100
Cincinnati (peds)- No home visits	Holtain Harpenden	ST Scaletronix (children) Scale-tronix 4800 (infants)	Dinamap GECarescape V100

5.K Policy of Duality of Interest

5.K.1 General Principles

The validity of research studies depends on investigator objectivity, and the general acceptance of research study results depends on the perception of investigator objectivity. Dualities of interest can be critical to both of these considerations since they can lead to or create the perception of bias. Dualities of interest may arise from interactions between investigators/research personnel and organizations such as private corporations, scientific or medical societies, and non-profit groups. Accordingly, the ASSESS-AKI Consortium must ensure that interactions and/or relationships with industry or other groups outside of the study organization do not influence (or appear to influence) the objectivity of the ASSESS-AKI decision making processes.

Loss of objectivity can result from financial conflicts and other factors and relationships. For example, scientific judgment can be affected by considerations of career standing. Not only can objectivity be diminished by such situations, but also commitment to the research endeavor.

Dualities of interest can involve a research organization rather than an individual investigator. Financial or other interests can conceivably affect the objectivity of a research group. This type of potential duality of interest must also be considered in the conduct of research studies.

Dualities of interest are not prohibited; however, it is imperative that real, possible, or potential dualities be declared to ensure objectivity and maintenance of individual and organizational integrity. While the process utilized to develop ASSESS-AKI studies should diffuse the potential impact of any duality that exists for an individual member of the ASSESS-AKI Consortium, it is the position of ASSESS-AKI Consortium that disclosure of any duality that exists or arises for a member will add assurance that ASSESS-AKI studies have been conducted in a fair and scientifically sound manner, devoid of inappropriate influences or the appearance of inappropriate influences. In order to attain further objectivity, the ASSESS-AKI Consortium will require management of dualities of interest when it is deemed necessary.

5.K.2 Definitions

Duality of Interest means a circumstance in which financial or other considerations can affect scientific objectivity or commitment to a research endeavor.

Research is a systematic investigation designed to develop or contribute to generalizable knowledge.

Investigator means principal investigator, co-investigator, and any other person at the institution who is responsible for the design, conduct or reporting of research. For the purposes of financial interest, "investigator" includes the investigator's spouse and dependent children.

Study-related entity means an entity with an active or potential interest in the conduct or outcome of an ASSESS-AKI Consortium study because:

a. a drug, biological, device or other product ("product") of the entity is a topic of research in the ASSESS-AKI Consortium study

b. a drug, biological, device or other product of the entity is a direct alternative or substitute for the product that is the topic of research by a Consortium study, or;

c. a drug, biological, device or other product of the entity is being used in the study (e.g., as a tool or as an adjunct, but not as a primary study drug) at a time in its scientific or commercial development that would play a substantial role in its commercial viability and success).

d. the impact of the use of the enterprise's product by the ASSESS-AKI or the outcome of ASSESS-AKI research may reasonably be expected to have a very significant impact upon the value of an investment

Financial interest means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria). It does not include indirect financial interest through broadly diversified instruments, e.g., in broadly diversified mutual funds and retirement plans.

Significant financial interest means financial interest in a business enterprise or entity if:

a. the value of the interests plus payments for services (but not the reimbursement of reasonable directly incurred costs) exceeds $10,000 per annum, or;

b. equity interest exceeds $25,000 (e.g., stocks, stock options, or other ownership interests); intellectual property rights (e.g., patents, copyrights, and royalties from such rights),

Other significant relationships with a study-related entity include:

a. research, training or other support from the entity for an ASSESS-AKI investigator, or in which the ASSESS-AKI investigator is involved, or over which the ASSESS-AKI investigator has control, responsibility for conduct, responsibility for making appointments, or the like, even if funding is not to the ASSESS-AKI investigator;

b. possible other relationships in which there is or seems to be dependency relationship of the ASSESS-AKI investigator to the study-related entity;

c. current or proposed participation in a clinical trial funded by non-NIH sources, which addresses a research question with close similarity to a proposed ASSESS-AKI Consortium study.

5.K.3 Policy

This policy and its definitions (e.g., financial interest, significant financial interest, other significant relationship, and study-related entity) shall be public information and shall refer to interests/relationships over the two calendar years prior to disclosure.

The existence (but not the amount or details) of any financial interest, any significant financial interest, and any other significant relationship of any ASSSESS-AKI Consortium investigator or any exception to the standard policy in any ASSESS-AKI Consortium study shall be public information. The existence of a significant financial interest and other significant relationships shall routinely be acknowledged in publications or as otherwise required.

A master list including financial interests, significant financial interests, or other significant relationships will be prepared by company name listing all of the PI/co-investigators who have involvements with the individual companies.

Recommendations concerning potential conflicts of interest will be the responsibility of the ASSESS-AKI Steering Committee (SC), which is comprised of the four ASSESS-AKI Principal Investigators, the Steering

Committee Chair, and the NIDDK Steering Committee Members. The Chair will supervise the review of disclosure documents and will oversee discussion and adjudication of potential conflicts by the ASSESS-AKI Principal Investigators. Upon review of a particular potential conflict of interest, the SC PIs will decide the level of participation and involvement the individual with the potential conflict may have with a particular study, on an individual case basis.

In general, no member of the ASSESS-AKI Steering Committee or co-investigator at a given center shall participate as an investigator or as a co-author in a for-profit company study with a research question similar to the one undertaken by the ASSESS-AKI. Permission by the Steering Committee to participate in such a study by an investigator with a potential conflict may be given and shall be public information.

Steering Committee members shall neither review nor rule on potential conflicts from their own ASSESS-AKI center.

In general, a member of the Steering Committee who has no potential conflict of interest with a study-related entity should conduct negotiations with a particular company (e.g. to obtain drug for a study, or to acquire equipment for the ASSESS-AKI). A person with a potential conflict should not have any involvement with certain entities (e.g., a biomarker company) regarding the specific project (e.g., negotiations for supplies) without the permission of the Steering Committee. The Steering Committee can waive this restriction based on the nature of the study, the role of the investigator, and the type of involvement.

Anyone with a significant financial interest, or other significant relationship (as defined above) must have at least one non-conflicted Co-PI involved with any study in which the individual with the conflict is permitted (by the Steering Committee) to participate. The Steering Committee can waive this restriction based on the nature of the study and the role of the investigator.

Permission by the Steering Committee to participate in a study by an investigator with a potential conflict shall be public information.

Relationships of investigators with study-related entities (and representatives of these entities) shall also adhere to the following principles:

ASSESS-AKI Consortium-related activities shall be discussed only as needed by the study and in the role of, or on behalf of, the ASSESS-AKI activity, but never in the context of other discussions, relationships, or interest that the investigator and that entity may have.

ASSESS-AKI study protocol and policies relating to the release of information dictate the confidentiality of non-publicly released information, as well as the release of certain confidential information to certain interested entities. Investigators must adhere to these policies. Except in a formal role, on behalf of the study, they must scrupulously avoid transmitting information to any entities that have interest in the study and they must be particularly scrupulous in avoiding such release of information to an entity in which the investigator has a financial interest.

To avoid conflicts of interest, every attempt will be made to offer companies participation on an open basis without specific product selection unless a specific product is deemed preferable by the group for patient safety, efficacy or convenience. If one product is indeed deemed preferable by vote of the Steering Committee, then a careful analysis for potential conflicts of interest will take place. Investigators must be cognizant of and adhere to federal regulations on the prohibition of "insider trading."

5.K.4 Obligations to ASSESS-AKI Regarding Dualities of Interest

All ASSESS-AKI participants are responsible for adhering to the ASSESS-AKI Duality of Interest Policies and Procedures with regard to their participation in ASSESS-AKI activities. Investigators, Associates, Support Staff, and others engaged in ASSESS-AKI research studies are to provide assurance that they will comply with the ASSESS-AKI Duality of Interest Policies and Procedures by completing all of the applicable Duality of Interest Disclosure forms. They are required to disclose real or perceived dualities between proposed research and financial interests, intellectual property and personal interests. The forms require a description of participation in outside activities, including employment, consultancies, stock ownership and intellectual property rights.

It is often difficult for a researcher to determine the extent to which disclosure is necessary. Each of the Duality of Interest forms includes specific criteria for guidance. However, the researcher must ultimately decide whether a product of a commercial entity is or isn't related to ASSESS-AKI research. In making this decision, the researcher should decide whether such a relation could reasonably have impact on objectivity or the appearance of objectivity in the performance of the research.

Involvement in outside professional or commercial activities should not delay or inhibit the publication of scholarly research or the sharing of information derived from such research. Where appropriate, as with clinical trials, ASSESS-AKI participants are expected to disclose relevant outside consulting arrangements or affiliations in their published scholarly works. This is now routinely imposed by some journals.

It is expected that all ASSESS-AKI participants will be in full compliance with all relevant DHHS, NIH and FDA policies regarding duality(ies) of interest (also known as "conflict(s) of interest").

5.K.4.a Obligations to Home Institution

In addition to complying with the ASSESS-AKI Dualities of Interest Policies and Procedures, ASSESS-AKI participants must comply with all of their local and institutional requirements regarding duality of interest (also known as "conflict of interest" at some institutions) and disclosure.

Any possible Duality of Interest relating to human subjects protections must be promptly and routinely disclosed to ASSESS-AKI and the ASSESS-AKI participant's Institutional Review Board (IRB) when seeking IRB approval for any ASSESS-AKI study. The same disclosure is required when a study has already been approved by an IRB and there are any changes in status pertinent to a Duality of Interest.

If the participant's home institution determines that it is necessary to manage a Duality of Interest pertinent to ASSESS-AKI, the participant is to inform the ASSESS-AKI Steering Committee and the NIDDK Project Officer immediately.

5.K.5 Process

Conflict of interest forms will be completed annually. Each investigator is responsible for identifying for review those related financial interests that meet criteria (a) or (b) under significant financial interest, and those which, although not meeting these criteria, raise issues that might reasonably be expected to raise concerns. Any other significant relationships with study-related entities must be described at least briefly, but in sufficient detail so that their acceptability can be assessed.

The potential for conflict of interest will be reviewed and whenever new protocols or products, or relationships with new entities are considered by the ASSESS-AKI Consortium, or if an investigator develops or terminates an ASSESS-AKI significant (or potentially significant) financial interest or such

interest changes. Potential conflicts of interest involving immediate family members of the participating investigators should also be identified.

Annually, and at the beginning of any new protocol, PI/co-investigators will notify the Steering Committee of any changes in their disclosure statement, and any potential conflict of interest will be reviewed by the Steering Committee.

The principal investigator at each ASSESS-AKI Clinical Research Center shall be responsible for transmitting to the Data Coordinating Center not only his or her own disclosure statement, but those of others at his or her institution that may fulfill the criteria of the participating investigator. The disclosure material must include a list of study-related entities in which there is a financial interest or with which there is another significant relationship, the basis and nature of the interest or relationship, and its classification as "significant financial interest" or "financial interest" and/or "other significant relationship." Steering Committee members shall neither review nor rule on potential conflicts from their own ASSESS-AKI center. In general, if the committee feels that there is a potential conflict of interest, the investigator involved will excuse himself or herself from all discussions and decisions pertaining to the ASSESS-AKI protocol.

The investigator is responsible for identifying for review any related financial interests that do not meet specific criteria under significant financial interest or other significant relationship (particularly other significant relationship criterion c), but for which reasonable persons might have differing judgments as to meeting these criteria. Any other significant relationships with study-related entities must be described at least briefly, but in sufficient detail so that their acceptability can be assessed.

Exceptions may be made in circumstances where both the substance and the appearance of the conflict are each sufficiently small and benefits to the study and the public outweigh these factors. If an exception is sought to this stated policy, the basis for it must be indicated. Participation by exception to standard policy shall be public information.

If the Steering Committee permits an investigator with a potential significant conflict to participate in discussions and decisions regarding a specific protocol and entity, the potential conflict shall be announced to and reviewed with the Steering Committee before the discussions commence.

The recommendations of the ASSESS-AKI Steering Committee shall be conveyed by the Chair to the NIDDK. In granting a waiver to the policy, the Chair and/or the NIDDK may seek independent review and advice from outside sources, if that process is deemed necessary.

Disclosure statements shall be kept within a secure file at the Consortium's Data Coordinating Center following review by the Board.

ASSESS-AKI Consortium publications should have a written disclosure statement, along the lines currently required by the New England Journal of Medicine.

5.K.6 Frequency of Documentation of Dualities of Interest

All individuals on the ASSESS-AKI SC (both voting and ex-officio members) are required to complete all Duality of Interest Disclosure forms initially and at all subsequent SC meetings that are attended. In addition, there is to be a disclosure when there has been any change in the status of a Duality of Interest.

If a change in the status of a Duality of Interest is disclosed when a SC meeting convenes, the individual is required to inform the Study Chairman who will decide whether it is necessary to implement special procedures regarding the Duality of Interest. The decision of the Chairman should be recorded in the minutes of the SC proceedings.

Investigators involved in proposal of a study are required to complete the appropriate Duality of Interest disclosure form before formal submission. Before a final protocol is approved, all research personnel subject to Dualities of Interest must complete the appropriate form. They are required to disclose any change in status on the appropriate form on an annual basis thereafter.

Dualities of Interest should also be considered when ASSESS-AKI committees and subcommittees meet to formulate scientific policies and develop protocols. Thus, Dualities of Interest should be disclosed at the beginning of each of these meetings (including teleconferences) and such disclosures should be recorded in the minutes. If a member of a committee or any other investigator feels that disclosure is insufficient for the management of a Duality of Interest, or if any questions arise, the Chair of the Steering Committee should be contacted.

All records of Dualities of Interest will be kept in a database at the Data Coordinating Center. Records of Duality of Interest for specific studies will be maintained for at least three years after the completion of each study.

5.K.7 Voting and Reviewing Protocols

One can only vote on or review an ASSESS-AKI protocol if there is no Duality of Interest. All potential voters and reviewers will receive prior notification of commercial entities that are associated with protocols. Any potential voters or reviewers who have a Duality of Interest must excuse themselves.

5.K.8 Violations of Duality of Interest Policy and Its Management

Violations involving duality of interest that could lead to removal from ASSESS-AKI activities include but are not limited to:

- Failure to disclose a Duality of Interest pertinent to ASSESS-AKI
- Failure to disclose to the home institution and/or its IRB a Duality of Interest pertinent to ASSESS-AKI
- Unwillingness to comply with management of a Duality of Interest that is requested by the Steering Committee
- Refusal to comply with ASSESS-AKI Dualities of Interest Policies and Procedures

When a possible violation is discovered, the Steering Committee formally conducts a review. The Steering Committee decides whether a violation has occurred and how it should be addressed.

If the Steering Committee decides to remove the ASSESS-AKI participant, or take another action, it is to inform that participant in writing. Such decisions can be appealed by the participant in writing within ten days of notice. The appeal is reviewed by the Steering Committee.

5.K.9 Duality of Assessment Score

The classification scheme below is intended to serve as a guideline for reviewing Dualities of Interest for ASSESS-AKI. The weighting of the Duality is somewhat arbitrary. Thus, the score should not be the only basis for the assessment of a duality.

5.K.9.a Nature of the Drug or Device with which the Individual is Involved

8 Protocol-specific product of company

5 Protocol-related product of company but not specific to protocol

2 Another product of same company but not protocol-related

5.K.9.b Nature of the Financial Interest

10 Majority ownership

9 Intellectual property>$10,000

8 Intellectual property<$10,000

8 Stock ownership>$10,000

7 Stock ownership<$10,000

5 Consulting and/or honoraria>$10,000 over 2 years

4 Consulting and/or honoraria<$10,000 over 2 years

3 Research funding>$30,000 over 3 years

2 Research funding<$30,000 over 3 years

5.K.9.c Role of an Individual in the Study

10 Principal Investigator for entire study

7 Principal Investigator for site

3 Researcher but not Principal Investigator

5.K.9.d Status of an Individual within the ASSESS-AKI Organization

9 ASSESS-AKI Principal Investigator or Chair

6 Others on ASSESS-AKI Executive Committee

3 Members of SC

2 Support staff

5.K.9.e Status of an Individual within Commercial Entity

10 CEO

9 On Board of Directors

6 On Scientific Advisory Committee

5.L Publication and Presentation Policy

The success of the ASSESS-AKI Study will depend largely on the number and quality of its scientific

publications and presentations. The purpose of the policy established herein is to encourage and facilitate the presentation of ASSESS-AKI Study analyses while providing guidelines that ensure appropriate use of the ASSESS-AKI data, timely completion of manuscripts and presentations, equitable access to authorship, and adherence to established principles of authorship.

Proposals for manuscripts resulting from data generated as a result of participating in the Consortium and all ancillary studies shall be submitted for review to the Publications and Presentations Committee (Pub-Pres C) and require approval by the SC before establishment of a Writing Committee or a submission for publication or presentation. It is anticipated that PIs of approved ancillary studies will lead at least one scientific paper emerging from the ancillary study analyses as specified in the Publications and Presentations Policy. Each manuscript and abstract would be expected to include an ASSESS-AKI investigator. The phrase "ASSESS-AKI" should be included in the title in all scientific presentations and manuscripts and listed as a key word whenever possible. Manuscripts will also contain an appendix listing ASSESS-AKI investigators who are deemed appropriate.

5.L.1 Types of Manuscripts

There are two manuscript types*, Core Study Manuscripts* and *Ancillary Study Manuscripts.*

- *Core Study Manuscripts.* Core Study Manuscripts analyze data collected as part of the Core ASSESS-AKI data set, and directly derive from the ASSESS-AKI Core study aims as described in the ASSESS-AKI Study Protocol, which includes manuscripts that address both primary and secondary objectives of the study. The Pub-Pres C has developed a summary of core manuscripts that address the six specific aims of ASSESS-AKI. These manuscripts are listed in Appendix B.
- *Ancillary Study Manuscripts*. Ancillary Study Manuscripts will be based, in part, on data elements originating from the specific aims of approved ancillary studies, regardless of the funding mechanism, as well as manuscripts from the parent studies of the Clinical Research Centers that directly incorporate data established through ASSESS-AKI activities.

5.L.2 Publications Policy Principles

- Publication policies should promote scientific inquiry within and productivity from the ASSESS-AKI Study.
- Abstracts, presentations, and publications based on ASSESS-AKI material must be accurate and objective and must not compromise the scientific integrity of the ASSESS-AKI study.
- The publications arising from the ASSESS-AKI Study should avoid overlap and conflicting representation of ASSESS-AKI Study findings.
- Recognition through authorship will be distributed fairly among the ASSESS-AKI Investigators.
- For ASSESS-AKI Study papers directly addressing a specific aim from the main protocol or from an ancillary study that uses data or samples from all clinical sites, authorship should include the PIs from all clinical sites or their designees, the NIH, the SC Chair, and the DCC, if such individuals indicate an interest and commitment.
- The ASSESS-AKI Study promotes the career development of trainees and junior faculty by providing them appropriate opportunities to lead and to be recognized as co-authors of ASSESS-AKI publications.

- Authorship on ASSESS-AKI publications will adhere to the most current Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors found in Appendix A.

5.L.3 Guidelines Regarding Manuscripts Published Prior to the Main Manuscripts

- No manuscript that reports on incidence or progression of CKD or on cardiovascular outcomes including heart failure, MI, and stroke may be published prior to the main ASSESS-AKI manuscripts addressing these outcomes.
- Any submitted proposal would be vetted by the ASSESS-AKI Steering Committee to decide if there is overlap with the ASSESS-AKI main specific aims.
- ASSESS-AKI will provide a time table on when it will have sufficient power to analyze these outcomes. These calculations would be updated on a bi-annual basis and would provide a time table to those submitting proposals to inform them regarding feasibility.
- Data could be released to requestors prior to publication of the main manuscripts, but there would be an embargo on actual submission until the main manuscripts are accepted for publication.

5.L.4 ASSESS-AKI Investigators

To assist in selection of Writing Committee members when more candidates are identified than can be accommodated, a priority ranking can be used as follows: first – ASSESS-AKI PIs, second – ASSESS-AKI Core Investigators, and third – ASSESS-AKI Team Members. This priority ranking is meant to be a general guideline.

a. ASSESS-AKI PIs
   - ASSESS-AKI Principal Investigators (including DCC)
   - NIDDK Project Scientist
   - SC Chair

b. ASSESS-AKI Core Investigators
   - Investigators who are Key Personnel for the ASSESS-AKI sites

c. ASSESS-AKI Team Members
   - Investigators with a more limited role.
   - Trainees and Research staff (including coordinators)

5.L.5 Ancillary Study Investigators Procedures

a. The manuscripts proposals can be developed by several mechanisms. These include, but not limited to,
   - the Pub-Pres C recommending Writing Committees for topics
   - unsolicited proposals by ASSESS-AKI Investigators or Non-ASSESS-AKI investigators
   - SC recommendations for creating a manuscript

b. For the list of core manuscripts listed in Appendix B, each investigator (including PIs and all co-investigators) will indicate their interest in working on the manuscript, specifically whether they would like to 1) lead the writing committee, 2) participate as a member of the writing committee, or 3) have no interest in working on the specific manuscript. Assignment of the first author and other members of the specific Writing Committees will be based on the investigators' level of interest and equitable assignment among the four consortium sites. Specific assignment will be done by a consensus of an Executive Committee consisting of the Steering Committee Chair, the NIDDK representative, and the DCC PI. Assignment to writing committees will be based on the interests of the investigators and no members will be asked to serve on a Writing Committee if they lack interest. Assignment will also consider when during follow-up there are adequate data for analysis and manuscript writing. The Executive Committee will attempt to distribute early and late manuscripts equitably amongst centers. For other manuscripts not included in the list of core manuscripts, the procedures outlined in section 3.G.2.c of the MOP will be followed.

c. It is expected that for the list of core manuscripts, once the Writing Committee has been formed, it will submit a manuscript proposal as outlined in Appendix A of the MOP, Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors, to the Pub-Pres C within 90 days. It should be noted that the Pub-Pres C has identified several manuscripts that can be prepared using current available data and these manuscripts will be given priority in terms of data analysis by the DCC and assignment to Writing Committees.

d. Once the proposal is submitted and reviewed by Pub-Pres C, the SC will provide final approval.

e. Submission of Proposals for Scientific Papers

- Proposals for manuscripts could arise from a number of sources
- The proposal must include "Summary Information" and a brief description of "Proposal Details" Using the ASSESS-AKI Manuscript Proposal Format See Appendix A
- The Pub-Pres C will review all proposals within two (2) weeks to verify use of the correct proposal format and to determine if there is specific, significant overlap with another paper or abstract in process, related to either the same outcome or to the same ASSESS-AKI biochemical/demographic/clinical factor.
- Upon approval by the Pub-Pres C, a manuscript number will be assigned to the proposal and it will be logged into a tracking system. A Writing Committee will then be assembled with the Writing Committee Chair taking responsibility for leading the preparation of the approved manuscript in a timely manner in collaboration with other committee members and the DCC (see Section 3.G.2.).
- The DCC will maintain records indicating the distribution of authorship by individual and location (Clinical Research Center, DCC, NIDDK, other).

5.L.6 Schedule for Manuscript Preparation

a. In general, the DCC will be expected to complete proposed analyses within two (2) months of the manuscript being approved if the data are available and the statistical plan agreed upon by the DCC and Writing Committee.

b. Initial Draft - within two (2) months after receipt of a set of complete analyses from the DCC.

c. Penultimate Draft - due no later than three (3) to four (4) months after the first draft is distributed to the Writing Committee.

d. Review by ASSESS-AKI PIs and/or designated core investigators who are not members of the writing group - within three (3) weeks of receipt. The Pub-Pres C and SC will provide final approval for submission of the manuscript

e. Verification by DCC – within two (2) weeks of receipt.

f. Submission to a Journal - Within thirty (30) days of receiving NIDDK and Pub-Pres C comments and verification confirmation

g. Response to each review. All members of the Writing Committee and Pub-Pres C need to approve of the response to each review before resubmitting the revised manuscript.

h. Manuscripts in Press. The corresponding author must obtain clearance from the Pub-Pres C Chair or his designee for submission of the corrections to the Galley Proofs. All authors will be provided with a copy of the Galley Proofs for review and approval; if no response is received within 48 hours, the author will be considered to have approved the proofs.

i. Non-adherence to the timelines outlined above may result in re-assignment of responsibilities to more interested committee members.

5.L.7 Abstracts and Presentations

a. The Pub-Pres C will approve final versions of all abstracts submitted on behalf of ASSESS-AKI.

b. Preparation and Submission of Abstracts for Scientific Meetings is allowed only for ASSESS-AKI data analyses. Data request to the DCC must be at least four weeks prior to presentation/submission deadline.

c. The full text of abstracts is due to the Pub-Pres C for review no less than two weeks before the abstract submission deadline.

d. Distribution of written handout material containing ASSESS-AKI data that have not been published is prohibited.

e. Accepted Abstracts and Invited Presentations. Copies of accepted abstracts or invited presentations must be submitted to the Pub-Pres C.

5.M Access to Study Data and Specimens

At the time of distribution of ASSESS-AKI specimens and/or information, the ASSESS-AKI collaborating investigator, with help from the DCC, will make explicit arrangements with the ancillary study PI for the security of these study materials and for their final disposition at the conclusion of the ancillary study. The safety and confidentiality of the ASSESS-AKI data at the collaborating institution is the responsibility of the ancillary study PI, as is the appropriate disposition of these materials after the study has been completed. Leftover DNA and laboratory specimens are destroyed or returned, and files of ASSESS-AKI data are returned or deleted, as established at the outset of the collaboration. An archival copy of the newly collected data and/or laboratory results not already held at the DCC will be sent to the DCC at the conclusion of the data analysis for and publication of the main (ancillary) study findings. This transfer is the responsibility of the ancillary study ASSESS-AKI collaborator(s). Once transferred back to the ASSESS-

AKI, these ancillary data will become part of the aggregate ASSESS-AKI data. Subsequent access to these data will be governed by the ASSESS-AKI Study Policy on Use of Archived Study Data and relevant requirements of the NIDDK Repository.

6 CLINICAL RESEARCH CENTER STANDARDIZATION

6.A Standardization of Clinic Procedures

Ongoing studies at the three CRCs will result in data accumulated by study personnel and derived from adhering to multiple procedures in the course of their responsibilities. By standardizing study procedures and requiring such data-gathering individuals to demonstrate the required level of procedure knowledge and competency, the opportunity for inconsistent data will be greatly reduced.

6.B Responsibilities and Qualifications of Coordinators and Data Entry Personnel

Personnel are required to successfully demonstrate competency to the satisfaction of an authorized qualified individual following the completion of a standard training procedure. In the case of personnel turnover during a study, replacement personnel shall complete standard training and certification prior to their participation in an ASSESS-AKI activity. The DCC is responsible for monitoring the certification progress of study coordinators and shall provide monthly certification status of all ASSESS-AKI coordinators.

The Quality Control Committee (QCC), with input from the SC, is responsible for all quality assurance aspects of the ASSESS-AKI Consortium. The QCC is described in Section 3.B.

6.B.1 Research Coordinator

The Research Coordinator shall be responsible for all study operations of his/her respective Clinical Research Center (CRC). The Research Coordinator will share all information related to specific tests and procedures including manuals of operation (MOP), forms, and training materials related to a protocol with study personnel (clinic coordinator, technicians, data entry personnel) as appropriate. The Research Coordinator has three mandatory certifications and several optional certifications.

Mandatory Certification:

1. ASSESS-AKI Consortium CRC operations training administered by the DCC.
2. Signed attestation of review of ASSESS-AKI protocol and training material.
3. For US sites: Completion of the NIH Human Subjects Training On-Line Course and/or Collaborative Institutional Training Initiative (CITI).
4. For Montreal Site: The MCH requires the following certification in clinical research.
5. For Ontario Site Ontario requires Tri-Counsel Policy Statement: Ethical Conduct for Research Involving Humans

6.B.2 Clinic Coordinators

The Clinic Coordinator, if assigned per protocol, shall be responsible for the performance of each protocol at each CRC conducting the protocol, but not for the study operation of the Center. There are two mandatory certifications and several optional certifications for the Clinic Coordinator.

Mandatory Certification:

1. Signed attestation of review of ASSESS-AKI protocol and training material.
2. For US sites: Completion of the NIH Human Subjects Training On-Line Course (http://phrp.nihtraining.com) and/or Collaborative Institutional Training Initiative (CITI– http://www.citiprogram.org/default.asp?language=english).
3. For Montreal Site: The MCH requires the following certification in clinical research: (http://ethique.msss.gouv.qc.ca/didacticiel/index.php?lang=en)
4. For Ontario Site Ontario requires Tri-Counsel Policy Statement: Ethical Conduct for Research Involving Humans (http://pre.ethics.gc.ca/english/tutorial/)
5. For Adult sites, coordinators must complete the TRAILS B training and submit appropriate paperwork to the DCC. Coordinators will receive notification of certification from the DCC to administer the TRAILS B.

6.B.3 Data Entry Personnel

Data entry personnel shall be responsible for entering data for the ASSESS-AKI Consortium studies.

Mandatory Certification for Data Entry Personnel:

1. Data entry by satisfactory completion of ASSESS-AKI DCC training or training received from an individual who has successfully completed data entry training

6.C ASSESS-AKI Clinical Research Center Operations Training and Certification

Consistency in performing protocol-defined procedures and recording study data strengthens the ability to achieve scientifically accurate outcomes. Therefore, it is crucial that research staff are trained and certified in all Consortium procedures. The DCC designs sessions to train the CRC staff in skills necessary to collect, record, and process protocol data, such as using the secure Consortium web site, recording data on the paper data collection forms, using the web-based data management system, and performing all Consortium procedures. The DCC will develop a one-day protocol training session as well as training via videoconference, or web-based training using CONNECT conferencing and presentation technology. When there is a turnover in the Lead Research Coordinator position at a CRC, the DCC will provide protocol and application training for the new Lead Research Coordinator who joins the ASSESS-AKI Consortium. Replacement personnel shall complete standard training and certification prior to their participation in an ASSESS-AKI Consortium study. Protocol training will use web-based training to maximize participation, be cost-effective, and be available to the other sites. Ideally, application training will take place at the DCC and will be funded by the CRC that sends the coordinator(s). If that is not possible, web-based training will be used.

Setting a date for the application training session should be initiated by the CRC. Application training will take place over a one-day period and will consist of the following:

1. Data Management Procedures
2. Data Entry System

6.D ASSESS-AKI Clinical Research Center Operations Training and Re-Certification

When a Research Coordinator/Clinic Coordinator is inactivated in the ASSESS-AKI certification module due to their departure from the ASSESS-AKI Consortium, the individual will need to review ASSESS-AKI procedures and have oversight/supervision by the Research Coordinator or other certified individual if they return to the ASSESS-AKI Consortium within two years.

6.E Human Subjects Protection Training

The NIH requires that ASSESS-AKI personnel complete Human Subjects Protection training. The original tutorial, exam, and certification documentation may be found at the NIH website at http//:ohsr.od.nih.gov. Clinical staff is encouraged to check with their institutions' Human Subject Protection Office (HSPO) to ensure they meet their institutional requirements. Clinical center staff must submit, to the DCC, documentation of the successful completion of either the NIH sponsored training or the training outlined by their institutions (HSPO).

6.F Site Visits

On-site reviews of Clinical Research Centers (CRCs) are intended to achieve the following goals:

- To assess the overall performance of the CRC, and the conduct of each ongoing protocol
- To assess the quality of data collection for current protocols
- To provide consultation in identifying and solving problems
- To transfer effective approaches from one CRC to another

Components of the site visit will include: meeting with personnel; examining facilities, including data files; reviewing administrative organization within the center; evaluating conduct of special procedures; auditing samples of medical charts and comparisons with entered study data, and other activities proposed by the DCC, the NIDDK, and the EEP. A site visit report will be prepared with specific recommendations.

The site visit team will include representatives from the DCC, the NIDDK, and possibly other CRCs. Other site visitors may include a member of the ASSESS-AKI Consortium EEP and a PI or Research Coordinator from an ASSESS-AKI CRC other than the one being site visited. The Quality Control Committee will assist the DCC in planning and performing site visits to each CRC. The DCC will prepare site visit reports which may include specific recommendations for the center. The report will be sent to the PI and Research Coordinator at the CRC where the site visit was performed, NIDDK, the Chair of the SC, and the EEP. If serious problems are detected, the report will also be sent to the QCC for review.

Each CRC will be site-visited, as necessary, during the nine-year project period.

7 RECRUITMENT

7.A TRIBE-AKI – Yale University

Yale will recruit 200 AKI participants and 200 non-AKI participants from the parent TRIBE-AKI study, with a current plan of 300 adults and 100 children. On day 3 or 4 of hospitalization, each participant will be screened by research personnel for feasibility of long-term follow-up and asked for permission for future contact. Information on two additional contacts names/numbers will also be obtained at this time. If the participant agrees to long-term follow-up, the following steps will be initiated.

(1) Every month, a Co-Investigator will query the "TRIBE_AKI" on-line database for all participants with AKI and all eligible non-AKI participants matched for the pre-specified criteria with the index participant with AKI.

- Eligible participants with non-AKI will be "ranked" for each in order from best match to worst match for each participant with AKI in the new time period.

(2) Materials to be mailed to all potential AKI and non-AKI participants considered eligible for long-term follow-up will be prepared approximately one month before the three-month visit. The mailing will include a thank you letter, tri-fold flyer containing explanation of the long-term study, and a "Certificate of Appreciation."

(3) One week after the mailing, research personnel at each site within TRIBE-AKI will call eligible participants.

- All adult participants with AKI will be contacted, unless targets for spectrum of severity are lagging (see Protocol, Section D.5), in which case only higher spectrum of severity AKI participants will be contacted and enrolled.
- In order to enrich the number of participants with severe AKI, additional possible AKI participants for ASSESS-AKI will be identified by screening the cardiothoracic intensive care unit at the participating TRIBE-AKI sites for patients who experience clinical AKI after undergoing cardiac surgery or aneurysm repair. These patients will be approached on the day their serum creatinine concentrations meet AKIN Stage 1 criteria. They will be asked by our coordinators about their willingness to participate in the ASSESS-AKI study. If they agree, then they will be enrolled into TRIBE-AKI. Their enrollment status will be entered into our online database.
- Adult participants will be contacted in order from highest number of matching criteria to lowest until the participant is secured for a three-month visit.
- Participants will be given a choice of follow-up at the research clinic or in their home.
- At the three-month visit, study personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.
- All children, of both AKI and non-AKI status, who agree to long-term follow-up, will be identified, contacted, and followed.

7.B VALID – Vanderbilt University Medical Center

Vanderbilt will recruit 250 adult AKI participants and 250 matched adult non-AKI participants from the ICU's and hospital floors at Vanderbilt and the local VA Medical Center (Tennessee Valley Healthcare System –

Nashville Campus); including but not limited to those enrolled in VALID. Hospitalized patients will be screened daily. Patients meeting inclusion/exclusion criteria outlined in the protocol will be enrolled into the proposed study based on assessment of AKI versus non-AKI status. Serum creatinine data will be extracted from the electronic medical record to assess for the presence of AKI. The VALID study currently enrolls patients within 24 hours of admission to one of four intensive care units on a daily basis: The Trauma Intensive Care Unit (TICU), Medical Intensive Care Unit (MICU), Cardiovascular Intensive Care Unit (CVICU) and Surgical Intensive Care Unit (SICU). Patients already enrolled into the VALID study will be screened using ASSESS-AKI inclusion/exclusion criteria to determine eligibility. For patients who do not receive their outpatient care at VUMC, informed or surrogate consent will be required in order to obtain information regarding baseline creatinine defined by the ASSESS-AKI protocol from their outpatient provider.

Once potentially eligible participants are identified:

- Research personnel will enroll subjects into the study and a copy of the informed consent will be provided.
- On a continual basis, all eligible AKI and non-AKI participants will be entered into the "VALID-AKI" matching database to be "ranked" based on the most mandatory and priority criteria fulfilled.
- Upon discharge, materials will be mailed to all eligible AKI and non-AKI participants including a thank you and welcome letter, a tri-fold flyer containing explanation of the long-term study, and a "Certificate of Appreciation." Participants will be given one week to consider the study before requesting the return of the informed consent.
- Within one week following the mailing of materials, eligible patients will be contacted by telephone to determine continued eligibility and schedule the three-month visit.
- Patients will be contacted in order from the highest to lowest number of matching criteria until a participant is identified for the three month visit.

7.C Kaiser Permanente of Northern California

Kaiser will recruit 157 adult AKI participants and 157 adult matched non-AKI participants from up to five Kaiser medical centers (Oakland, San Francisco, Walnut Creek, and Hayward) as described below:

<u>For AKI participants:</u>

- Research personnel will go to each recruiting hospital and after confirming access to the AKI participant, obtain written consent from the participant to complete a short questionnaire, to obtain a single non-fasting blood specimen and random urine sample, and to confirm the participant's agreement to be contacted within the next 30 days to discuss the study further.
- Within 30 to 45 days after hospitalization, a follow-up letter from the CRC PI will be sent to each AKI participant enrolled during the acute hospitalization to introduce the long-term study protocol.
- One week after sending the letter, research personnel will call the AKI participant to screen for remaining eligibility and to schedule the three-month visit.
- At the three-month visit (conducted at a central research clinic in Oakland), research personnel will obtain written consent for participation in the long-term study and conduct the three-month visit

protocol on the same day.

- Research personnel also will review the consent at the 12-month follow-up visit to reinforce the schedule and study protocol with the participant.

For non-AKI participants:

- After an AKI participant successfully completes a three-month study visit, research personnel will identify a pool of up to ten possible matched controls who are hospitalized within a recent time frame of the enrolled AKI participant.
- Prior to hospital discharge, research personnel will go to each recruiting hospital and after confirming access to the potential non-AKI participant, obtain written consent from the non-AKI participant to complete a short questionnaire, to obtain a single non-fasting blood specimen and random urine sample, and to confirm the participant's agreement to be contacted within the next 30 days to discuss the study further.
- Within 30 to 45 days after hospitalization, a follow-up letter from the CRC PI will be sent to each non-AKI participant enrolled during the acute hospitalization to introduce the long-term study protocol.
- One week after sending the letter, research personnel will call the non-AKI participant to screen for remaining eligibility and to schedule the three-month visit.
- At the three-month visit, research personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.
- Research personnel also will review the consent at the 12-month follow-up visit to reinforce the schedule and study protocol with the participant.

7.D University of Washington

The University of Washington will recruit 200 adult AKI participants and 200 matched adult non-AKI participants from the ICU's at Harborview Medical Center. Patients in the trauma, surgical, and medical ICU's will be screened daily for inclusion/exclusion criteria. The CRC will seek IRB permission to initiate collection of samples before consent has been obtained. This will allow the CRC to enroll patients who are too ill to provide consent but are without local surrogates. If consent is not obtained, these samples will be destroyed.

Patients/surrogates will be approached for possible consent into the ASSESS-AKI study on day 1 of their hospitalization. Upon this initial contact, the CRC will ask for consent for participation in a short questionnaire, collection of study samples, and permission for further contact for long term aspects of the study. The CRC will obtain additional contact names/numbers as well. The CRC anticipates two possible scenarios for the consent process of study subjects.

Cohort 1:

1. For those patients with a pre-hospitalization creatinine within the past 365 days documented in the medical record, immediate enrollment into the study can occur. Sample collection will be initiated and serum creatinine data will be extracted from the electronic medical record to assess for the presence of AKI.
2. Patients in whom surrogate consent is obtained during hospitalization will need to provide informed

consent by the three-month visit and efforts will be made to obtain consent before hospital discharge. Patients unable to provide informed consent by the three month visit will be ineligible for the longitudinal study.

3. The CRC anticipates that given the proposed matched parallel cohort design, we will be enrolling both AKI participants (those who experience AKI) and non-AKI participants (those who do not suffer an AKI episode) and will ultimately be matched on a minimal set of key confounding characteristics per study protocol.

Cohort 2:

1. For patients without a pre-hospitalization creatinine, the CRC will ask for consent as noted above, and will additionally ask for signatures on a Release of Medical Information form so that primary care or referral providers may be contacted for potential creatinine values within the past year. If obtained, verification that creatinine values were obtained from IDMS-standardized laboratories will occur. Sample collection will be initiated. If creatinine values are unable to be determined, these subjects will not be contacted for the follow up portion of the study.
2. If surrogate consent has been obtained, subjects will be re-consented before discharge and concurrently approached for consent to place their samples and data in the University of Washington KRI Data and Biosample Repository.

Within 1-3 weeks following discharge, materials will be mailed to all potential AKI and non-AKI participants enrolled during the acute hospitalization to introduce the long term follow up protocol. The mailing will include a thank you letter plus a flyer containing explanation of the long-term study. One week after mailing, research personnel will call eligible participants to answer potential questions, screen for remaining eligibility, and invite them to attend the three-month study visit.

At the three-month visit (conducted at the University of Washington KRI facilities and laboratory or in patient home), research personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.

8 PARTICIPANT RETENTION

	Yale-Cincinnati	Yale-Ontario	Yale-Montreal	Yale-New Haven	Vanderbilt	Kaiser	UW
Verify/Update address and phone numbers at every visit	X	X	X	X	X	X	X
Send Reminder letters/reminder phone calls prior to appt.	X	X		X	X	X	X
All mailings sent "certified mail"	X						
All mailings signed by PI and Project Manager	X		X	X	X	X	X
Schedule study visits to coincide with clinic visits	X		X		X		X
Offer parking /transportation reimbursement		X	X	X	X	X	X
Offer flexible visit schedule/call times to complete visit	X	X	X	X	X	X	X
Offer Home Visits		X	X	X	X		X
Offer 'finger-pokes' instead of venipuncture		N/A	X	N/A	N/A	N/A	N/A
Send Participant/PCP Test Result Letters		X		X	X	X	X
Utilize Child Life	X	N/A		N/A	N/A	N/A	N/A
Birthday/Holiday Cards	X		X	X	X	X	X
Give gift card and yearly gift for in-person visit	X		X	X	X	X	X
Give small gifts at V3M, V24M, V36M		X	X	X			X

Certificate of Appreciation/Welcome Letter	X	X		X			X
ASSESS AKI Newsletter	X		X	X	X	X	X
Cultivate trusting relationships with Participants	X	X	X	X	X	X	X

8.A Participant Retention and Tracking

To maximize participant retention, we will employ several successful strategies that have been employed in various prospective cohort studies, including the CRIC Study,[91] AIDS cohort study,[92] Nurses' Health Study,[93] and the Women's Health Initiative Clinical Trial and Observational Study.[94] Use of some of these strategies has yielded a long-term success rate of >90% at three years in the CRIC Study,[91] 89% at 9.5 years in the Multicenter AIDS Cohort study,[92] 90% success rate at eight years in the Nurses' Health Study,[93] and 97% at ten years in the Women's Health Initiative Study.[95]

These include having a single Research Coordinator as the primary contact, who will develop a long-term relationship with participants to enhance attendance at follow-up visits. The following additional tracking and retention strategies will be used to augment this relationship and to maintain long-term contact with and follow-up of study participants:

- Attempts to obtain Social Security Number information that will be used for ascertaining vital status among participants who are lost to follow-up. It will be optional for participants to provide this information.
- Phone and address listings for subjects and contacts will be updated at each interaction (visits/phone).
- Personalized letters and notes from the PI and Research Coordinator will be sent.
- Study newsletters (providing information on the study progress and results, along with general and kidney-specific health messages) will be mailed. Personalized birthday and holiday greeting cards will be sent.
- Approximately two to four weeks prior to the time for the follow-up visits, a phone call will be placed to the participant to schedule the date and time of the appointment.
- A reminder letter with the date, time, and location of the visit may be sent to the participant immediately after the visit is scheduled.
- Proxy interviews to collect primary outcomes will be conducted if the participant is deceased or has diminished cognitive functioning.

In addition, there will be site-specific efforts to enhance participant retention.

TRIBE. Additional strategies include the following: (1) a thank you letter, along with a certificate recognizing their participation, and a tri-fold pamphlet with study name, logo, information, study processes, and contact numbers and photos of the investigators and coordinators will be sent eight weeks after

discharge from the hospital; (2) research visits will be offered to be conducted in the participants' homes for participants who cannot drive to the research unit; (3) an annual Renal Health Assessment by a Yale Nephrologist will review relevant clinical and laboratory tests and provide any guideline-based recommendations; (4) reimbursement for time, travel and parking.

VALID. Additional strategies will include (1) Reimbursement for time, travel, and parking; (2) an annual Renal Health Assessment by a Vanderbilt Nephrologist who will review relevant clinical and laboratory tests and provide guideline-based recommendations; and (3) a thank you letter along with a certificate recognizing their participation.

Kaiser. Two additional strategies will be employed including (1) providing an annual Renal Health Assessment by a Kaiser Nephrologist who will review relevant clinical and laboratory tests and provide any guideline-based recommendations; and (2) monthly review of the Kaiser membership list to determine membership status of enrolled participants.

We will also employ the following strategies to trace hard to find and lost participants:

- Extended search will be initiated for those who cannot be reached, including contacts with personal contacts and the primary care physician.
- US postal service will be contacted for current address (National Change of Address system).
- Use of reverse telephone directories and other online reference data sources.
- National Death Index[96] will be searched for the occurrence and potential cause of death among participants who are considered lost to follow-up. This will be facilitated by requesting collection of social security number information from participants upon enrollment into the long-term study. It is recognized that there is a significant temporal delay in the availability of data from the National Death Index, so Social Security Administration vital status files[97] will be another complementary source given that it is updated quarterly.

Washington. Two additional strategies include the following: (1) a thank you letter and pamphlet with study name, logo, and information including contact numbers and photos of investigators and coordinators will be sent post discharge; (2) will offer to coordinate research visits with return physician visit appointments if patient prefers, will offer parking validation, and also the choice for the visit to take place in the participants' homes for their convenience.

8.B Participant Withdrawal

It is anticipated that over the course of time, a small number of ASSESS-AKI participants may withdraw from the study. This may occur officially by formal written notification from the participant to a CRC PI, or unofficially when a participant cannot be reached via the usual methods of contact and in whom death cannot be confirmed. Every effort will be made to ensure high rates of long-term retention and to acquire complete data on all participants (see Section 8. A).

Participants who relocate to an area from which it is no longer feasible to travel to a CRC will be asked to permit study personnel to contact them annually for a telephone contact follow-up. Centers may offer inducements to participants who drop-out or relocate in the form of additional travel reimbursement in return for their continued participation.

9 COMPUTING AND NETWORKING ENVIRONMENT

9.A Computer Network

The ASSESS AKI Consortium consists of the Data Coordination Center (DCC) and four Clinical Research Centers (CRC) (Yale CRC consists of five sites) connected using the Internet and the World-Wide Web. The computer network provides electronic communications and data exchange among the group members.

The computer network permits study data transmission, facilitates electronic mail, management of problematic events, and facilitates the exchange of information on program management, policy information, and manuals of operations. The network uses the World-Wide Web, a technology that supports an easy-to-use, cross-platform, graphical interface to collect and disseminate ASSESS AKI study data.

Each site makes use of an existing local area network within the individual site locale. There is one level of access to the ASSESS AKI Consortium information. This web site provides secure web access for Research Coordinators and Principal Investigators and is designed to facilitate easy dissemination of study information, reports, and data. The DCC has established that the minimally configured personal computer required to connect to the DCC shall be an IBM-compatible computer running Windows XP and using Internet Explorer 8.0 or higher. Each site will be responsible for purchasing and maintaining the equipment required and paying any network fees. Data transmissions over the network will be encrypted using a 2048-bit Secure Sockets Layer (SSL) encryption standard. The SSL protocol provides data security layered between application protocols (such as Hypertext Transfer Protocol (HTTP) and Transmission Control Protocol/Internet Protocol (TCP/IP)). The security protocol provides data encryption, server authentication, message integrity, and optional client authentication for a TCP/IP connection.

The DCC maintains a user helpdesk to assist each site when computer problems arise with accessing the secure website. Study Site personnel will contact the DCC helpdesk via the web site (completing the web form), email (helpdesk), or telephone to initiate a process to correct a problem. The DCC has voicemail for after-hours problem reporting, and the problem will be addressed the next business day.

Maintaining network security is paramount. The Department of Public Health Science's network is located behind a firewall, the first line of defense in protecting the data. An Internet firewall is designed to reject attempts from outsiders trying to gain access to an institution's computer. This level of security rejects network access attempts from outside the network and prevents any unauthorized individuals from gaining access to the ASSESS AKI study information or computers. In addition, all users desiring access to the level one portion of the web site must obtain a username and password from the DCC (refer to section 9.B.2).

The DCC uses an Oracle Database management system to provide several additional levels of authentication. Database authentication works like basic authentication and uses username/password information stored in the database but enables the DCC to permit access to information based upon pre-defined roles.

9.B Secure WebAccess Site

Features of the ASSESS AKI WebAccess site include: access to the ASSESS AKI data entry application (refer to section 10.A.), visit packets, standard forms, Steering Committee meeting minutes, telephone lists, etc.

9.B.1 Computer Requirements for Accessing the WebAccess Site

- An IBM compatible PC running Microsoft Windows XP.
- Microsoft Internet Explorer 8.x or higher, capable of 2048-bit encryption. Adobe Acrobat Reader 8.0 or higher is required to view PDF files via the secure web site.
- Microsoft Office is needed to view any Word, PowerPoint, or Excel files which may be posted to the web site.

THINGS TO NOTE:

- These system requirements were previously tested by the DCC. They provide optimal performance and compatibility; however other platforms and versions of software may also work adequately.
- If the application is not performing as expected and Internet Explorer 10 is being used, perform the following steps to remedy the issue.

  Open Internet Explorer 10

  Press the Alt key to display the Menu bar (or right click on the Address bar and then select Menu bar)

  Click Tools, and then click Compatibility View settings

  Add the website to the Compatibility View list.

9.B.2 Obtaining a User Name and Password for the WebAccess Site

- The Research Coordinator at the site will complete the User Account Checklist for the individual who is requesting access to the ASSESS AKI private web site. The checklist is available on the ASSESS AKI Web Access site located on the home page. If the employee cannot get access to the ASSESS AKI Employee Checklist, contact the DCC helpdesk via email (helpdesk), or via telephone.
- The individual who is requesting access to the ASSESS AKI private web site will receive e-mail confirmation of his/her assigned web site user name and temporary password. Individuals are required to change their passwords after the initial login, see section 9.B.4.
- KEEP YOUR USERNAME AND PASSWORD IN A SECURE PLACE. DO NOT SHARE YOUR USERNAME OR PASSWORD.
- Giving your username to anyone is a blatant security violation of your right to use the ASSESS AKI application.
- See section 9.C.

9.B.3 Logging into the WebAccess Site for the First Time

- Once the web site account is created, open your web browser.
- In your web browser, type the ASSESS website address into the address bar and press Enter.
- Type your user name into the “Username” field and then your password into the “Password” field.

- Click "Login" to log into the web site.

9.B.4 Changing your initial temporary password

- Once successfully logged into the ASSESS AKI WebAccess site for the first time, you will be forced to change your password.
- On the Change Password page, enter your new password in the first text field at the top of the browser window.
- Re-enter the same password again in the second text field to confirm they are identical.
- To save your new web site password, click the Change Password button under the last text field.

THINGS TO NOTE:

- Whenever changing your web site password, it will take effect immediately.
- The next time you log in, you must use your new password.

9.B.5 Logging Out of the Web Access Site

- To log out of the web site, click the "Log Off" link on the left-hand navigation bar.

IMPORTANT:
Log out of the web site whenever you are finished. Do not close your browser window or leave the ASSESS AKI WebAccess site until you have logged off.

9.B.6 Contacting the DCC for Help With Logging Into the Site

- If you have problems logging into the ASSESS website, click the 'Trouble Logging In?' link on the login screen. You will be asked to provide your username and an email will be sent to the email address associated with your username. The email will contain a link to reset your password and will be valid for 2 hours. The email link may only be clicked once within that 2 hour window.
- If you have tried to reset your password on your own and still cannot login:
  - Call the DCC Helpdesk
  - Send an email to helpdesk
  - Click on the 'Helpdesk Form' link in the footer of the login screen and submit a request to the helpdesk.

9.B.7 Password Management

- ASSESS passwords will expire every 90 days.
- Upon logging into the website, the application will check when a user's password will expire. If the user is within 15 days, s/he will receive an alert message that her/his password will expire in X number of days.
- The user can change her/his password at any time by clicking on 'Site Management' in the left hand navigation bar. Click 'Change your password' to get the correct screen.
- If a user's password expires, s/he will be forced to change the password before being allowed access to the rest of the website.

- Password requirements:
  - Must be at least 8 characters long
  - Must contain 3 of 4 types of characters:
    - Uppercase letters
    - Lowercase letters
    - Numbers
    - Symbols other than @ and _
  - Password cannot be reused within 540 days
  - Password may only be reused once

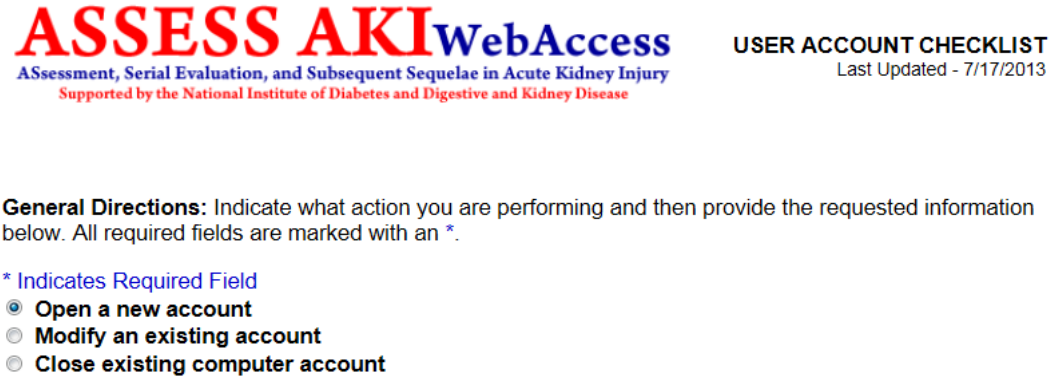
9.C User Account Checklist

9.C.1 Introduction

In order to gain access to the ASSESS WebAccess site, each employee must have a User Account Checklist submitted for them. This checklist collects 2 pages of information. The first captures basic contact information while the second asks detailed questions about what kind of access each employee needs. All of the responses are used at the DCC to create an entry in our ASSESS directory, add the employee's name to email aliases, and grant access to the website and data entry application. Each request is reviewed and approved by the project coordinator at the DCC before it is processed. Once a request is completely processed, the employee should receive an email notifying him/her of their username and password and/or new permissions.

9.C.2 Submitting a Checklist

The ASSESS User Account Checklist is available from the homepage under the DCC HelpDesk link after logging into the WebAccess site. Any user with access to the homepage may submit a request for a new account. Users with coordinator access to at least one protocol may submit a request for a new account, to modify an account, or to close an account.


ASSESS AKI WebAccess
ASsessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury
Supported by the National Institute of Diabetes and Digestive and Kidney Disease

USER ACCOUNT CHECKLIST
Last Updated - 7/17/2013

General Directions: Indicate what action you are performing and then provide the requested information below. All required fields are marked with an *.

* Indicates Required Field
- (•) **Open a new account**
- ( ) **Modify an existing account**
- ( ) **Close existing computer account**

9.C.3 Open a New Account

The user will select the 'Open a new account' radio button. The screen will display all of the questions listed in section 9.C.3. The user will complete the contact information and submit the form and the next screen will display all of the questions listed in section 9.C.4. After the user submits the application permissions

request, the request is sent to the DCC helpdesk and processed. The new employee will receive an emailed copy of the request and an email with his/her username and password once the request has been processed.

9.C.3.a Modify an existing account

Users must have coordinator access to at least one protocol in order to see the 'Modify an existing account' radio button. When the user selects that option, a new question will appear to ask what needs to be modified. The user will select Contact Information or Website and/or Application Permissions. The user will select Next.

If the user is modifying contact information, s/he should provide the name of the employee whose information has changed. Then the user should provide only the changed information and select Submit. An email notification will be sent to the DCC helpdesk and processed.

If the user is indicating that a last name has changed due to marriage or other reason, s/he should submit a modification to that user's contact Information. In the name fields, provide the original name and then enter a description in the Addition Instructions/Requests text box that indicates that his/her name has changed. Please provide a new email address in the work email field. The DCC will make the appropriate changes to the user's contact information and create a new user account and send an email notification when the changes have been made.

If the user is modifying website or application permissions, s/he will need to search for the employee being modified by providing the username and/or name of the employee. Partial information may be provided. For example, if the employee's last name is Smith, providing Smi in the Last Name text box will return the employee. The user has access to and can search for all employees within the same partnership. Once the search has been executed, the user should select the 'Edit Account' link next to the employee s/he wishes to modify.

The Application Permission screen will be displayed and will pre-populate with the permissions that the employee currently has. The user should modify the request and submit the screen. An email request will be sent to the DCC helpdesk and the employee will be notified when his/her permissions have been altered.

9.C.3.b Close an existing computer account

Users must have coordinator access to at least one protocol in order to see the 'Close existing computer account' radio button. When the user selects that option, the search screen will appear to allow the user to search for the employee who is leaving. Partial information may be provided. For example, if the employee's last name is Smith, providing Smi in the Last Name text box will return the employee. The user has access to and can search for all employees within the same partnership (Sites that begin with the same number are in the same partnership.). Once the search has been executed, the user should provide an Effective Date that the user will no longer need access and select the 'Close Account' link next to the employee s/he wishes to terminate. An email request will be sent to the DCC helpdesk and the request will be processed after the effective date has passed.

9.C.4 Contact Information

The items below represent and provide a brief description of each question listed on the Contact Information page of the ASSESS User Account Checklist.

Question #	Question Text	Description
1	Full Name	Please provide the first name, middle initial, and last name of the employee.
2	Title	Please provide the title of the position that the employee holds at your location.
3	Function/Role –	Please check off all roles that the employee will hold. More than one can be selected: PI/Co-PI – Investigator at a center Coordinator - Responsible for seeing participants, completing forms, resolving data errors, etc... Data Entry - Responsible for entering forms into the ASSESS application Lab Personnel - Responsible for receiving and/or receiving lab samples Other - Examples: individuals from the NIDDK, NHLBI, Visitor, EEA Reviewer or EEP
4	Personnel ID	Please provide a 4-digit number to identify this employee. The digit portion of the employee's center ID will be prepended to this number to create a 5-digit ID. This 5-digit ID will be used to track certification data for the employee and listed in the header information of a data collection form to indicate the employee who completed a procedure. This ID must be unique across the ASSESS network. If you are providing an ID that has already been used, you will receive an error message upon submitting the form.
5	Center	Please select the primary center that this employee is from.

6	Work Address	Please provide the physical and mailing addresses for the employee.
7	Work Phone	Please provide the work phone number for the employee at which the DCC or other network staff can reach him/her.
8	Cell Phone	Please provide the cell phone number for the employee at which the DCC or other network staff can reach him/her.
9	Pager Number	Please provide the pager number for the employee at which the DCC or other network staff can reach him/her.
10	Fax Number	Please provide the fax number for the employee at which the DCC or other network staff can reach him/her.
11	Work Email	Please provide the email address for the employee at which the DCC or other network staff can reach him/her.

General Directions: Please complete the name of the person for whom you are requesting the change. Then, complete **just the changed information**.

Contact Information:

1. **Full Name:*** First: Middle Initial: Last:
2. **Title:***

IMPORTANT: Please choose the role(s) that best represent you below. This will be used to set your permissions within the website and data entry application.

3. **Function/Role:** (Check all that apply.) ☐ PI/Co-PI ☐ Coordinator ☐ Other ☐ Data Entry ☐ Lab Personnel
4. **Personnel ID:** (This is a 4-digit ID that will identify all personnel for certification purposes. Examples include last four digits of SSN, employee ID, or other number user can remember.)
5. **Center:**
6. **Work Address:** Name of Institution:* Street:* City:* State:* Zip:*

   Mailing Address (if different from above) Street: City: State: Zip:
7. **Work Phone:***
8. **Cell Phone:**
9. **Pager Number:**
10. **Fax Number:**
11. **Work Email:***

Additional Instructions/Requests:

Cancel Reset Submit

9.C.5 Application Permissions

The items below represent and provide a brief description of each question listed on the Application Permissions page of the ASSESS User Account Checklist. All questions are asked if the user is creating a new employee checklist. However, if the user is modifying an employee, questions are different if the employee is a coordinator or a lab user. The table below shows the question numbers each scenario.

Question # for new employee	Question # for modifying coordinator	Question # for modifying lab user	Question Text	Description
12	1	1	Do you need access to the secure website? Check 'yes' if you need to access ASSESS forms, report, minutes, any part of the ASSESS application, etc…	If the employee needs to download anything from the ASSESS WebAccess Site or launch the data entry application, select 'yes'.
12a	1a	1a	These groups below control access to website content. Please select the groups that pertain to you. Note: This will be reviewed and approved at the DCC before granting access. (Centers, Committees, Miscellaneous) For site staff, do NOT select DCC, Admin, RC, NIDDK, QCC, CENTRAL LAB	This question is only displayed if the user selects 'Yes' to question 12 or 1. Website groups are granted permissions to folders on the website. The groups are listed as Sites, Committees, and Miscellaneous. The sites listed are filtered based on the partnership that the employee is in. Contact PIs are automatically granted access to all of the sites within their partnership. Site Directors are automatically granted access to their site only.

13	2	N/A	Do you need access to the application for participant enrollment, data entry, query resolution, and/or entry of biological samples or the ability to create sample shipments?	If the employee needs access to the data entry application for registry, participant enrollment, data entry, biological sample tracking, and/or query resolution, please select 'Yes'. If the user does not need access to the application, please select 'No'.
13a	2a	N/A	For which protocols? Adult sites, select '1'. Pediatric sites, select '2'.	This question is only displayed if the user selects 'Yes' to question 13 or 2. Please select which protocols the employee will be working on.
13b	2b	N/A	For which sites?	This question is only displayed if the user selects 'Yes' to question 13 or 2. Please select which sites the employee will be working at.
14	N/A	2	Do you need lab access for Biological Sample Tracking to mark samples as received? Note: If Yes, this means that you are an employee at one or more of the labs in Question 14a/2a and will be receiving samples from other sites. If you are not an employee at any of those labs, please change your response to 'No'.	Please select Yes if you are working a lab or your site has been selected to act as a lab for a protocol-specific sample.
14a	N/A	2a	For which labs?	This question is only displayed if the user selects Yes to question 14 or 2. Please select which lab the employee will be working at.

Current Permissions for AKI_CC1:

1. Do you need access to the secure website? Check yes if you need to access ASSESS forms, report, minutes, any part of the ASSESS application, etc... (●) Yes ( ) No

1a. These groups below control access to website content. Please select the groups that pertain to you. Note: This will be reviewed and approved at the DCC before granting access.

Centers	Committees	Miscellaneous
☐ YALE NEW HAVEN	☐ QCC	☐ ADMIN
☑ YALE		☐ CENTRAL LAB
		☑ NIDDK

2. Do you need access to the application for participant enrollment, data entry, query resolution, and/or entry of biological samples or the ability to create shipments? (●) Yes ( ) No

2a.* For which protocols?
- ☑ 1_ASSESS
- ☑ 2_ASSESS
- ☐ P91 Adult
- ☐ P92 Peds

2b.* For which centers?
- ☑ 1B Cincinnati
- ☑ 1C London
- ☑ 1D Montreal
- ☑ 1E New Haven
- ☐ 2A Vanderbilt
- ☐ 3A Oakland
- ☐ 3B San Francisco
- ☐ 3C Walnut Creek
- ☐ 3E Hayward
- ☐ 4A UW-Harborview

NOTE: If you need lab access for Biological Sample Tracking to mark samples as received and do not already have a lab account, please submit a new checklist. If you already have an account, please modify that account.

Current Permissions for AKI_CENTRAL_LAB:

1. Do you need access to the secure website? Check yes if you need to access ASSESS forms, report, minutes, any part of the ASSESS application, etc... (●) Yes ( ) No

1a. These groups below control access to website content. Please select the groups that pertain to you. Note: This will be reviewed and approved at the DCC before granting access.

Centers	Committees	Miscellaneous
	☐ QCC	☐ ADMIN
		☐ CENTRAL LAB
		☐ NIDDK

NOTE: If you need coordinator access to the application or center access to Biological Sample Tracking and do not already have an account for this, please submit a new checklist. If you already have an account, please modify that account.

2. Do you need *lab* access for Biological Sample Tracking to mark samples as received? (●) Yes ( ) No

Note: If Yes, this means that you are an employee at one or more of the labs in Question 2a and will be receiving samples from other sites. If you are not an employee at any of those labs, please change your response to No.

2a. For which labs?

- ☐ 95 - Rutgers Lab
- ☑ 96 - DNA - Central Lab
- ☑ 98 - Central Lab
- ☐ 99 - Bio Repository

9.D Accounts and Passwords Policy

9.D.1 Purpose

The purpose of this policy is to establish a standard for password management.

9.D.2 Policy

Access to the ASsessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury Consortium, (ASSESS AKI) stored in electronic format, must be safeguarded from unauthorized access through the assignment of unique user accounts that are password protected. Activity associated with an account is attributable to the assigned owner, and as such a password becomes a digital signature. Account owners must take reasonable measures to safeguard their account and passwords from unauthorized use and immediately report known or suspected compromises.

9.D.3 Person Responsible

All members of the ASSESS AKI Consortium

9.D.4 Procedure

Applicable to All Users

9.D.4.a Requirements

To reduce the likelihood of an electronic account being breached, the following measures must be taken:

- Do not share or reveal passwords.
- Do not store passwords in non-secure environments (e.g. under a keyboard) or electronically in unencrypted formats.
- Do not automate the entry of passwords (e.g. use of electronic scripts, auto logons, etc.).
- Immediately change passwords that are suspected or known to be compromised and contact the ASSESS AKI Helpdesk.
- Prior to a change in status (employment, work unit, student, etc.) initiate a review of systems access privileges and, where appropriate, request changes (modify, surrender) to existing accounts.
- Do not request others to share their password with you.

9.D.4.b Password Standards

The password management standard for the ASSESS AKI database management system is as follows:

1. Passwords must conform to the following standards
    - Contain three of the following categories of characters
        - Lower case letters
        - Upper case letters
        - Numbers (0-9)
        - Underscore (password may not begin with an underscore)
    - Be at least six characters in length; ideally, many more characters in length
    - Be significantly different than your UserID or Name
    - In general, should not be a password you have used in the past or use for other purpose

General Password Guidelines- All Users

- Do not base passwords on personal information (i.e. names: family, pets, sports teams, etc.).
- Do not create passwords that are a word in any language (slang, dialect, jargon, etc).
- Do not write down passwords.
- Change passwords on a regular basis.

QUESTIONS, CONCERNS AND EXCEPTIONS

For direction pertaining to your password or account, please contact the ASSESS AKI Helpdesk via email (helpdesk), or via telephone.

CORRECTIVE ACTION AND SANCTIONS

Individuals who fail to comply with this policy are participant to progressive disciplinary action. Repeat violators or willful misconduct may result in consequences such as:

- Mandatory participation in Privacy and Information Security training.
- Temporary or permanent restrictions of electronic access privileges.
- Legal action, potentially resulting in civil or criminal penalties.

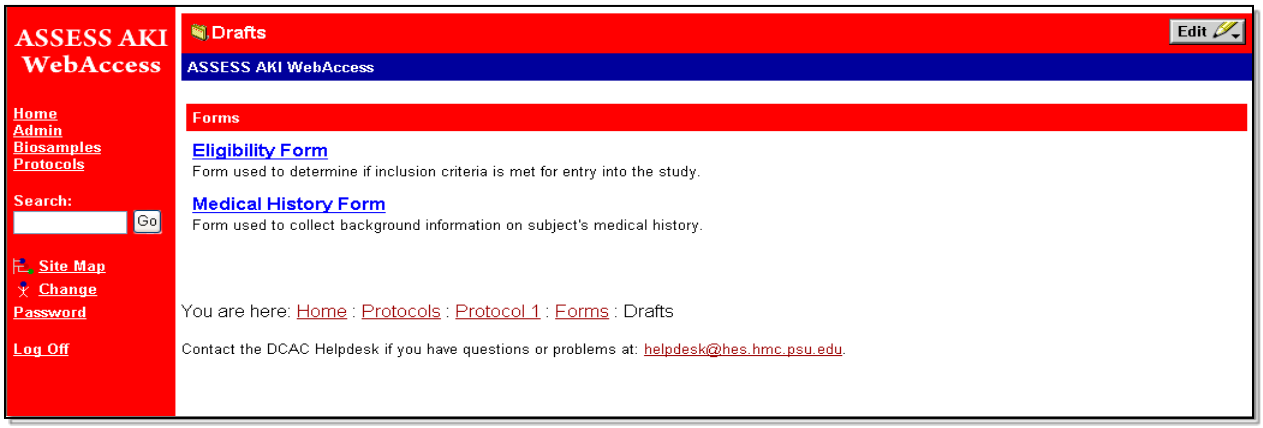
9.E Document Management System

9.E.1 Introduction

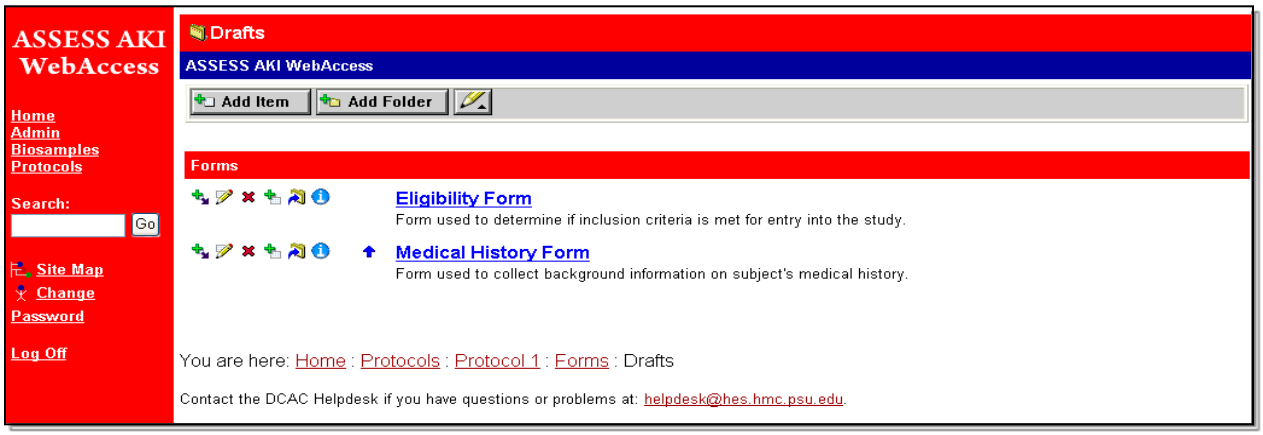
The ASSESS AKI secure website is used to collaborate on ideas in order to develop study designs, data collection forms, and Manuals of Operations (MOPs) as well as distribute information related to the consortium and protocols including minutes, contact information, study design, forms, and (MOPs). All website information is organized into a directory structure by creating folders and posting items into the folders, and each folder is represented to the user as a webpage. Access to items within the website is controlled at the folder level by granting users Read or Edit permissions. This section of the MOP is designed as a user manual to guide members of the ASSESS AKI Consortium in posting or modifying information on the secure website.

9.E.2 Editing a Folder

If a user has access to edit content within a folder, an Edit button will appear on the top right corner of the webpage. If a user does not have access to the Edit button and believes that s/he should, that user should contact the DCC helpdesk.



Selecting the button will place the user in Edit mode. Based on the permissions that the user has, s/he will have access to the 'Add Item', 'Add Folder', and 'Cancel Editing' buttons across the top of the webpage. The 'Add Item' button will allow a user to add a file, text, or URL to the current folder. The 'Add Folder' button will allow the user to create a subfolder within the current folder. The 'Cancel Editing' button will return the user to Read mode.



Once in Edit mode, the user will also have access to edit each item already posted on the webpage. There are several options available to the user to edit a specific item. Based on permissions and the status of the current item, not all icons will be available to the user.

Icon	Action	Description
	Add item below this item	Posting an item by using the 'Add Item' page will add an item at the bottom of the page. This icon allows the user to post an item directly below the current item.
	Edit this item	Allows the user to modify the existing item. If the item is a file, this will allow the user to upload a new version of the file.
	Delete this item	Allows the user to delete the item. If the item is a file, only the most recent version of the file will be deleted. Users may only delete versions that they have posted.
	Add a sub item below this item	Allows the user to post an item that will be attached to the current item. The sub item will be indented under its parent when displaying the webpage.
	Move this item to a different folder	Moves the item and any sub-items into a different folder. The user may only move items into folders to which s/he has edit permissions.
	View file history	Allows the user to view the different versions that have been posted to files.
	Unlock file	Allows the user to release a lock if the user currently has the file locked.
	Move this item up one level	Allows the user to reorder the items on a page.

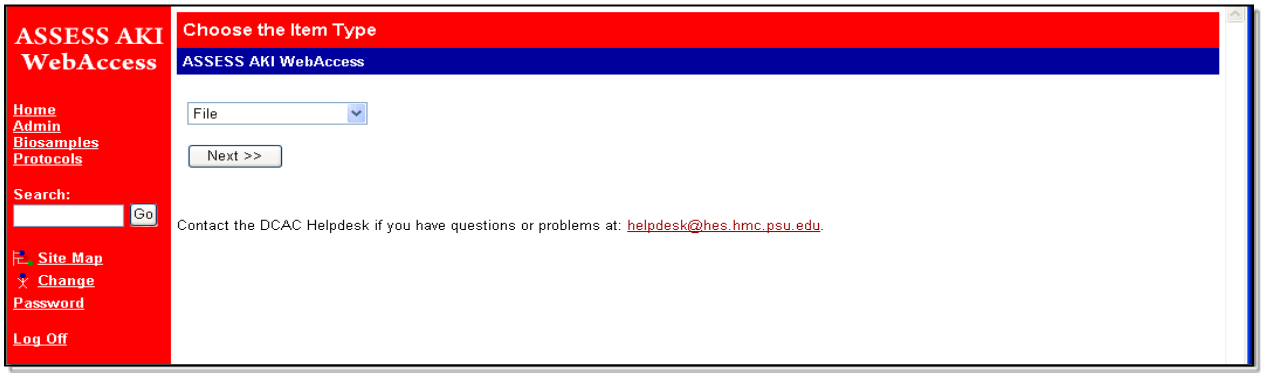
9.E.2.a Files and Versioning

Three types of items may be posted to the ASSESS AKI website. The most popular item type to be posted is a file. Users may post various types of items to the website including but not limited to .txt, .doc, .xls, and pdf files. Each file may be opened directly from the website or downloaded to the user's local computer.

If a file is modified, a new version may be uploaded to the website and the application will track the version number. The most recent version of a file will always be the file displayed for downloading, however users with editing permissions will have access to the older versions of the file as well as to the revision log.

Posting a file

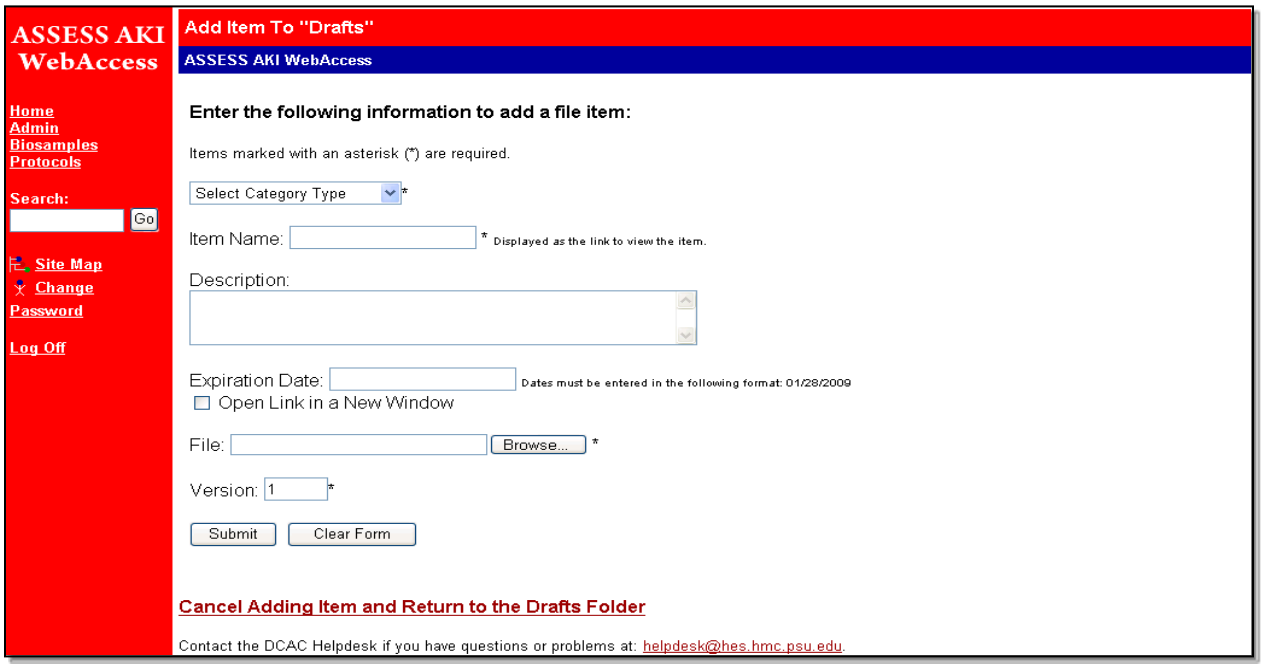
- To post a new file to the website, navigate to the folder in which you want the file to reside. Select the Edit button on the top right corner of the website.
- There are two ways to add a new file. By selecting the 'Add Item' button, you will add a file to the bottom of the items within that folder. If you want to add a file and have it displayed below a specific item already within that folder, selecting the icon will post a new item directly below the current item.
- Select File from the Item Type drop down box and select 'Next'.



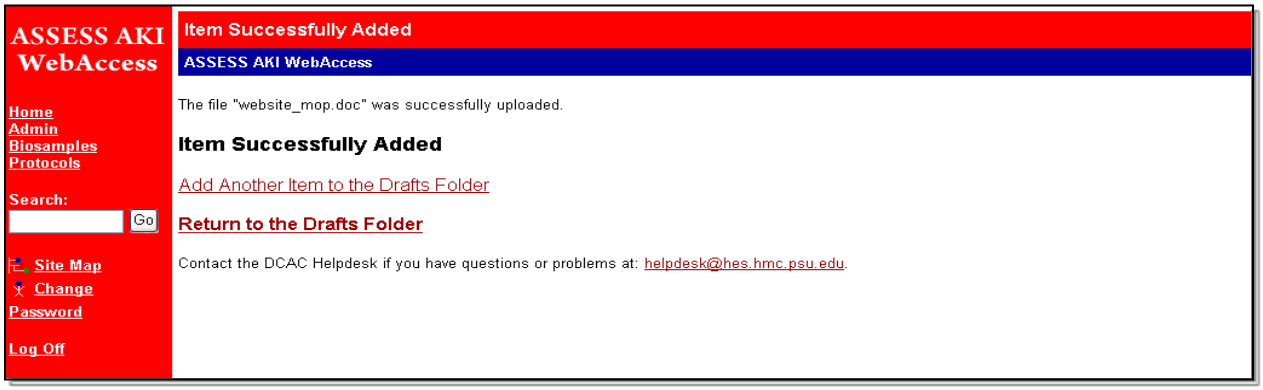
- Select the category type. The category is used to physically separate items posted to the same folder into different sections on the webpage. The category name appears in a red bar across the screen and items are then listed below the category. (Required)
- Provide a name for the file. The name of the file is displayed to the user as a link to open or download the file. (Required)
- Provide a description of the file. The description is displayed to the user underneath the file name. (Optional)
- Provide an expiration date for the file. After the expiration date has passed, the file will no longer be displayed on the website. (Optional)
- Indicate if the file should be opened in a new window. (Optional)
- Select the file to be uploaded. (Required)

- IMPORTANT: The website does not support new documents with an “x” on the end of the extension. For example only documents that are .doc or .xls are supported, but not documents that are .docx or .xlsx.

- Provide the file version. The default version number is 1; however this can be manually modified to match the version number printed on a document. (Required)
- Select the ‘Submit’ button.



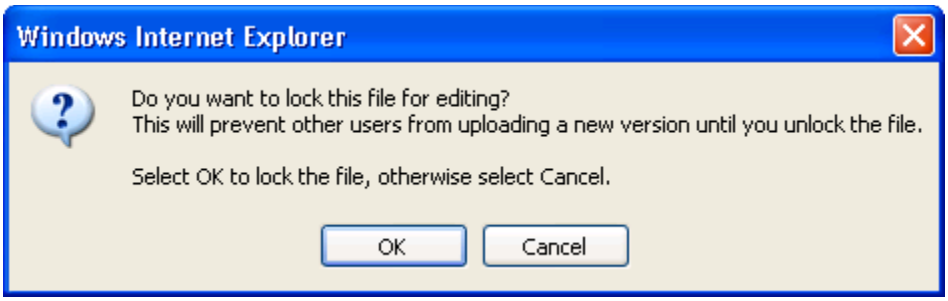
- If you have multiple items to post, select the link to ‘Add Another Item to the Folder’. Otherwise, select the link to ‘Return to the Folder’.



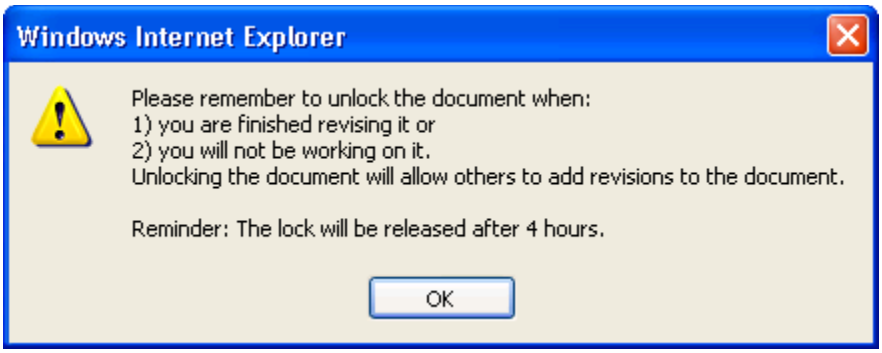
Locking Files

If a user is going to download a file to his/her local computer and make changes to it, s/he should lock the file. This will prevent other users from being able to upload versions to the website until the lock has been released, minimizing the chance of users overwriting each other's changes.

To lock a file, select the file name to download the file. A pop up box will appear and ask you if you want to lock the file for editing. Note: You do not need to be in Edit mode to lock a file. However, you cannot lock a file within a folder that you do not have editing permissions on.



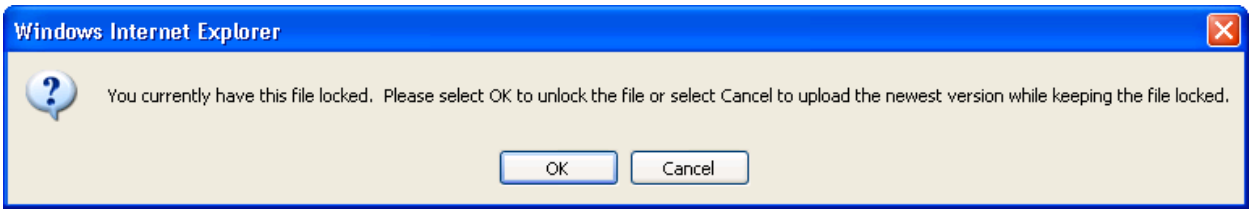
Once a file is locked, you will be reminded to unlock the file when you are finished making your edits.



IMPORTANT: Files will only remain locked for four hours to prevent a user from forgetting to unlock a file. After four hours have passed, the lock will automatically be released.

Unlocking Files

The user who owns a lock on a file may release the lock in two different ways. The first way is to select the icon that appears next to the file when in Edit mode. This will release the lock. The second way is to upload a new version of the file. After uploading the file, a message will pop up and ask the user if the lock should be released.



Files will automatically be unlocked after four hours to avoid a user from forgetting to unlock it. In addition, files may be unlocked by the site administrator at the DCC at any time.

Editing a File/Uploading a new Version

In order to change the information about a file (such as name or description) or upload a new file version, select the icon next to the file.

- Modify any of the following: Category, Item Name, Description, Expiration Date, and/or Open in new window. (Optional) Note: If you are just modifying this information, you do not need to upload a new version of the file.

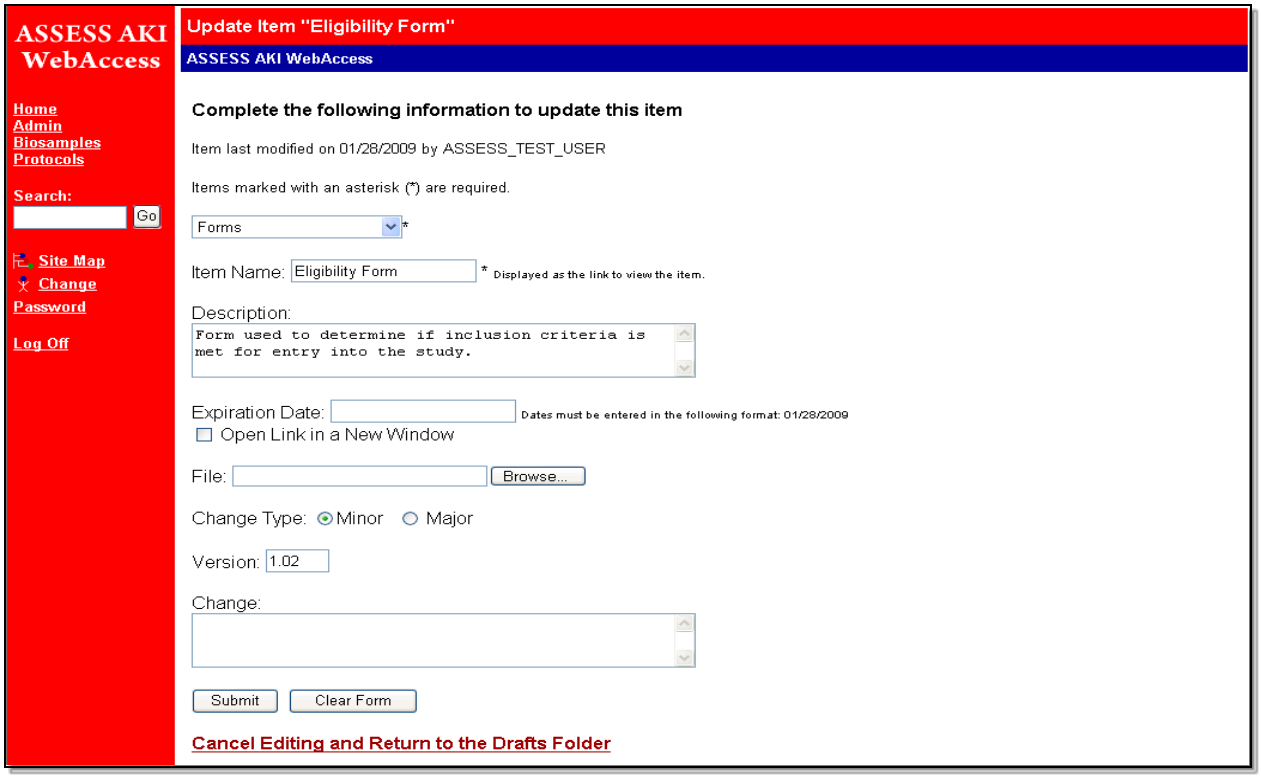
- If you are uploading a new version of the file, select the Browse button and select the new file. Doing this will activate the Version and Change text boxes for changes.

    - IMPORTANT: The website does not support new documents with an "x" on the end of the extension. For example only documents that are .doc or .xls are supported, but not documents that are .docx or .xlsx.

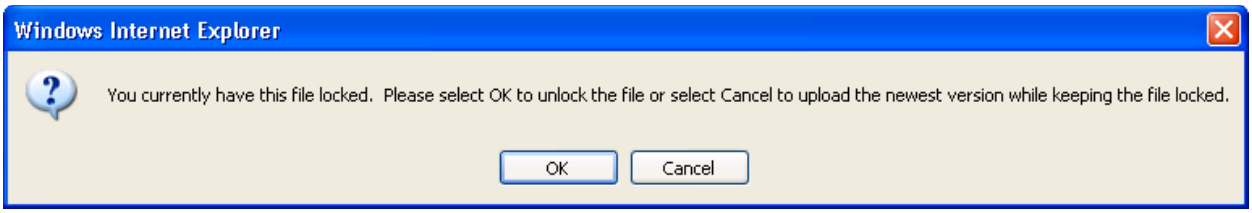
- The Change Type is used to determine the new Version number. Minor changes will increment the version by .01 while major changes will round the version to the next whole number. In addition, you may manually alter the version number provided that it is greater than the current version number. (Required if uploading file)

- Provide a description of what has changed in the document from the last version to the current version. This will be used to provide users with a log of the changes that have occurred in the document's history. (Required if uploading file)

- Select the 'Submit' button.



- If you currently have the document locked, you will get a prompt to unlock the document or keep it locked.



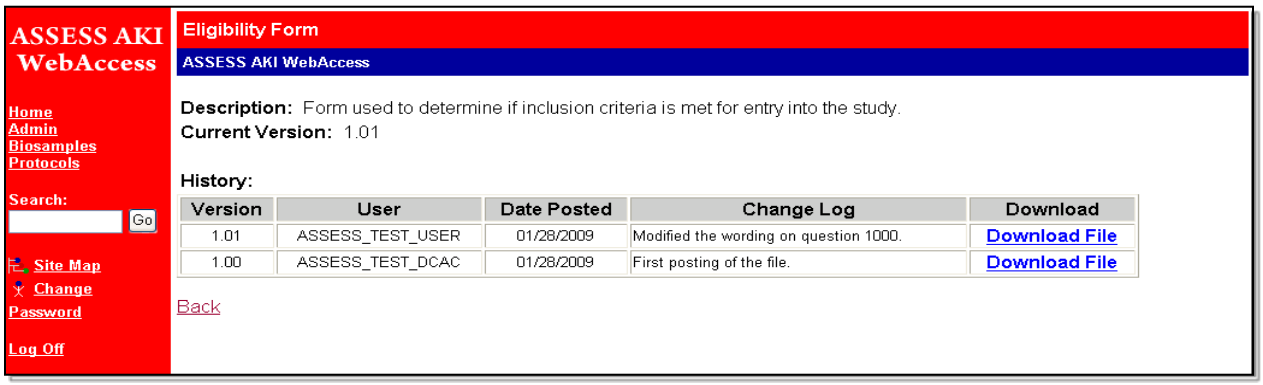
Deleting a File

In order to delete a file, select the icon next to the file. You will be taken to a new web page with a message indicating that you are about to delete the most recent version of the item and asking if you wish to continue. You have the option to continue the delete or cancel it.

- Only the most recent version of the file will be deleted.
- Users may only delete versions that they have posted.

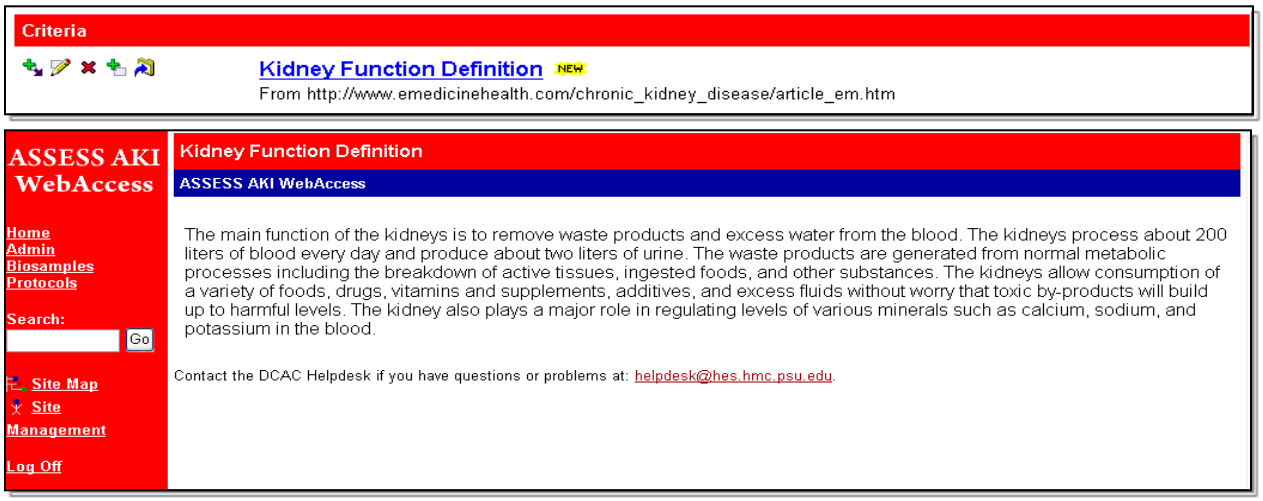
Viewing Versions

In order to view old versions of a file and see the revision history, select the icon next to the file. Old versions may be downloaded by selecting the 'Download File' link for the appropriate version.



9.E.2.b Text

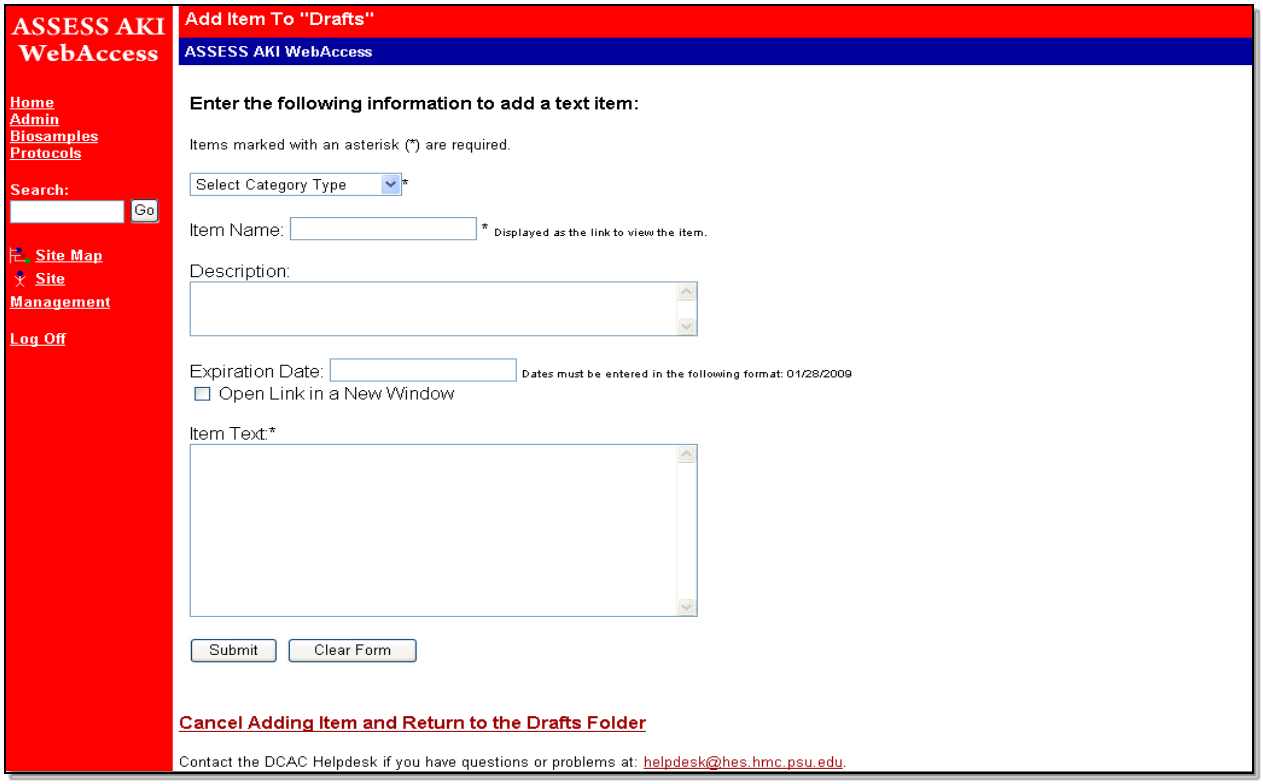
Text is another item type that can be posted to a folder. By selecting the link to the item, the text is displayed directly on the website instead of in a file format.



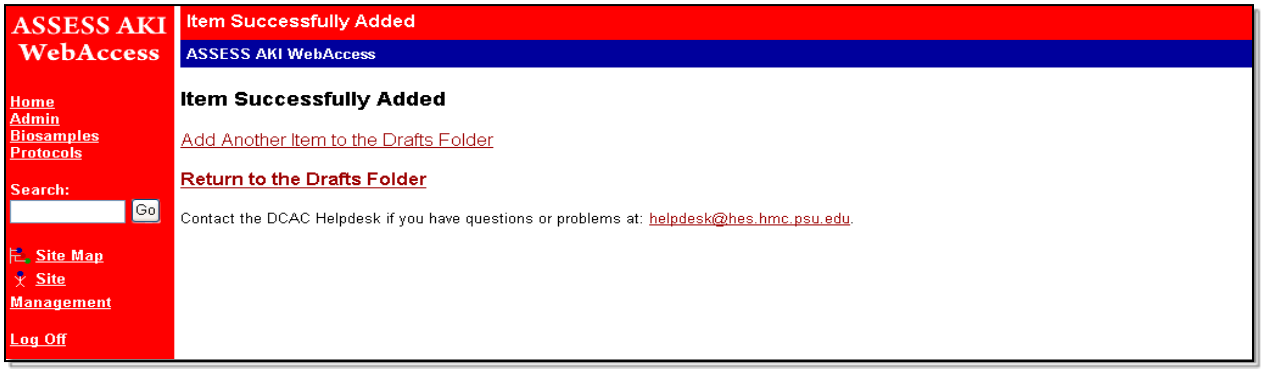
Posting Text

- To post text to the website, navigate to the folder in which you want the text to reside. Select the Edit button on the top right corner of the website.
- There are two ways to add new text. By selecting the 'Add Item' button, you will add text to the bottom of the items within that folder. If you want to add text and have it displayed below a specific item already within that folder, selecting the icon will post a new item directly below the current item.
- Select Text from the Item Type drop down box and select 'Next'.

- Select the category type. The category is used to physically separate items posted to the same folder into different sections on the webpage. The category name appears in a red bar across the screen and items are then listed below the category. (Required)
- Provide a name for the text. The name of the text is displayed to the user as a link to navigate to a page that displays the full text. (Required)
- Provide a description of the text. The description is displayed to the user underneath the item name. (Optional)
- Provide an expiration date for the text. After the expiration date has passed, the text will no longer be displayed on the website. (Optional)
- Indicate if the page that displays the full text should be opened in a new window. (Optional)
- Provide the full text description up to 1000 characters. (Required)
- Select the 'Submit' button.

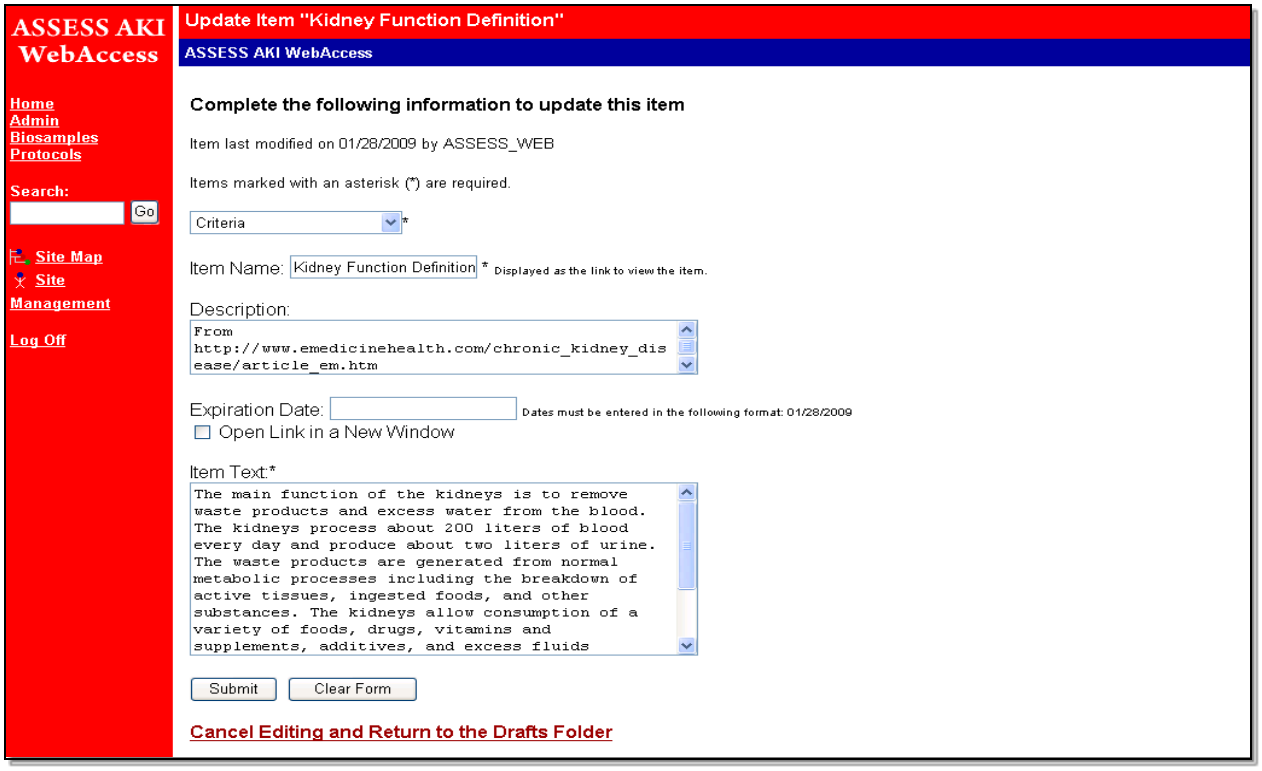


- If you have multiple items to post, select the link to 'Add Another Item to the Folder'. Otherwise, select the link to 'Return to the Folder'.



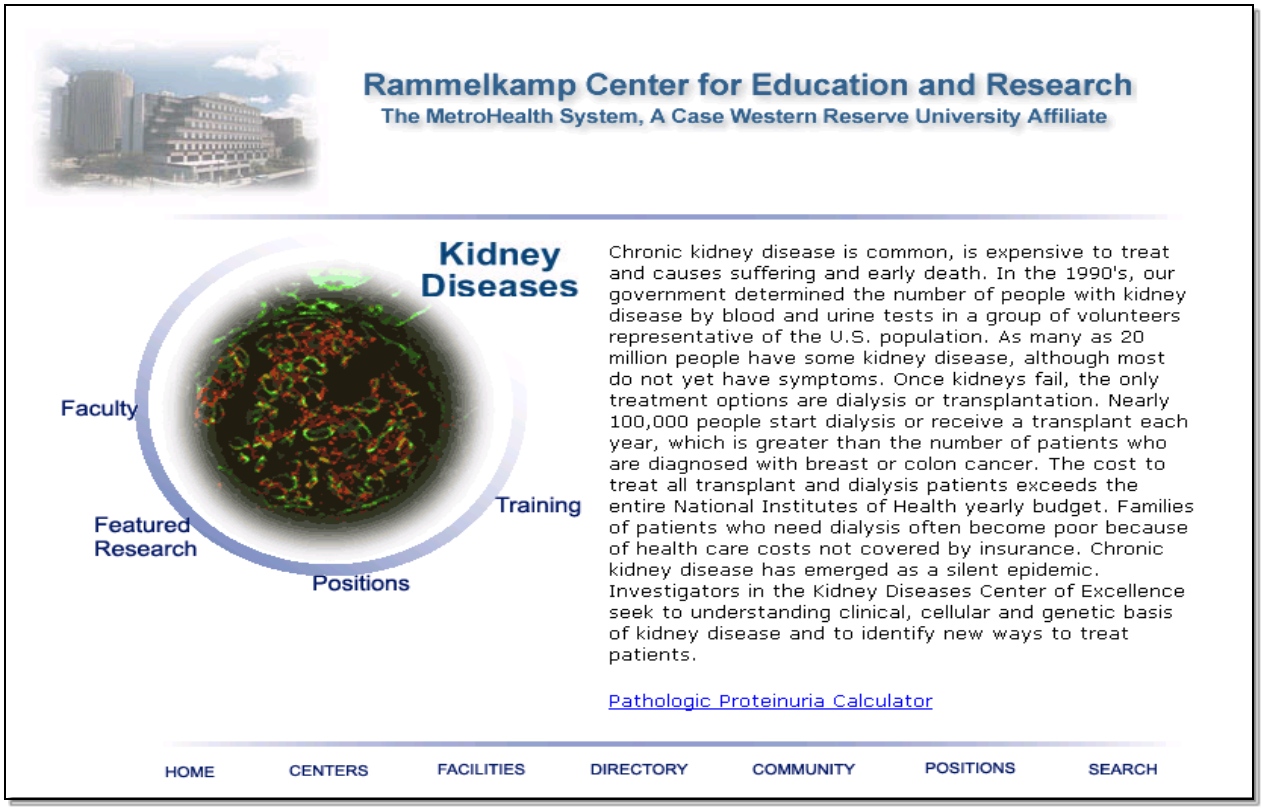
Editing Text

- In order to change the information within a text item, select the icon next to the item.
- Modify any of the following: Category, Item Name, Description, Expiration Date, Open in new window, and/or Item Text. (Optional)
- Select the 'Submit' button.



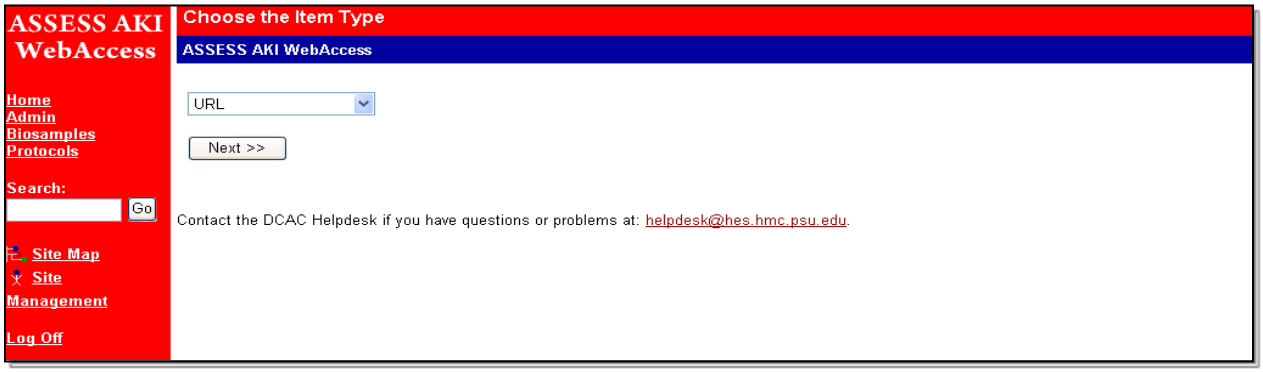
9.E.2.c URLs

A URL is the final item type that can be posted to a folder. By selecting the link to the item, the user is navigated to the URL that was posted.

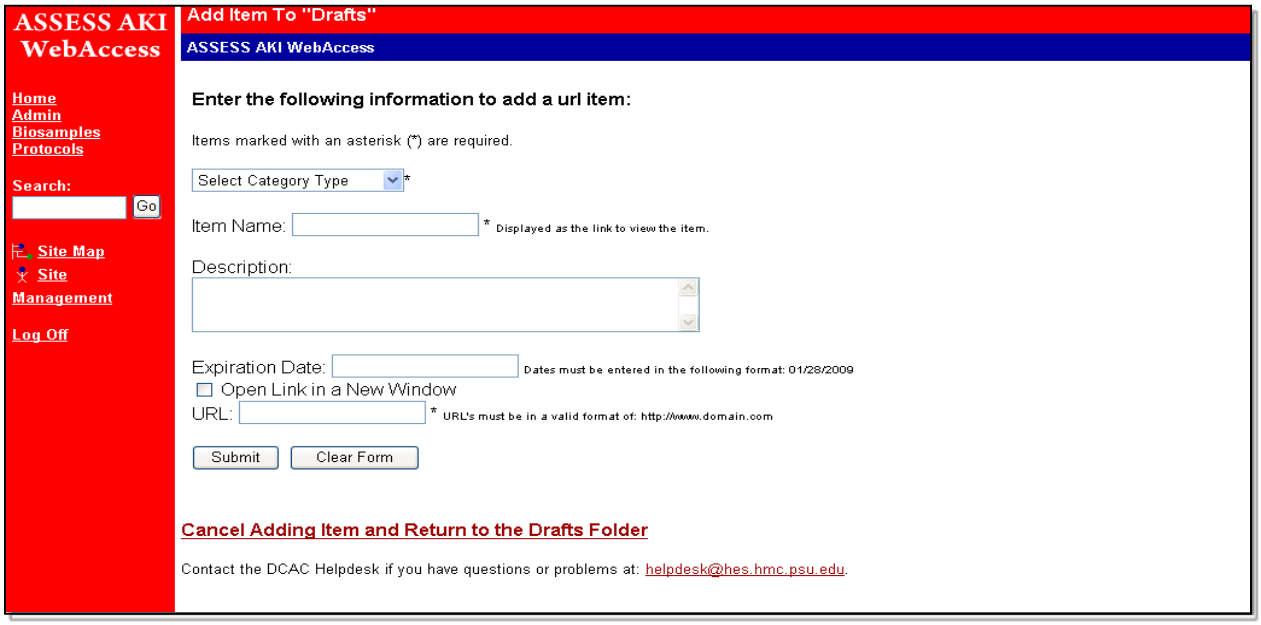


Posting a URL

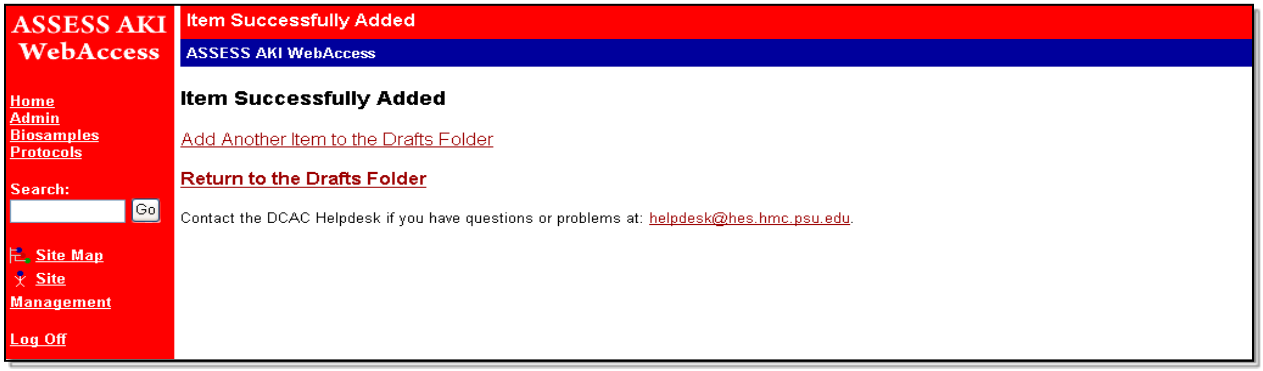
- To post a URL to the website, navigate to the folder in which you want the URL to reside. Select the Edit button on the top right corner of the website.
- There are two ways to add a new URL. By selecting the 'Add Item' button, you will add the URL to the bottom of the items within that folder. If you want to add the URL and have it displayed below a specific item already within that folder, selecting the icon will post a new item directly below the current item.
- Select URL from the Item Type drop down box and select 'Next'.



- Select the category type. The category is used to physically separate items posted to the same folder into different sections on the webpage. The category name appears in a red bar across the screen and items are then listed below the category. (Required)
- Provide a name for the URL. The name of the URL is displayed to the user as a link to navigate to the posted URL. (Required)
- Provide a description of the URL. The description is displayed to the user underneath the item name. (Optional)
- Provide an expiration date for the URL. After the expiration date has passed, the URL will no longer be displayed on the website. (Optional)
- Indicate if the URL should open in a new window. (Optional)
- Select the 'Submit' button.

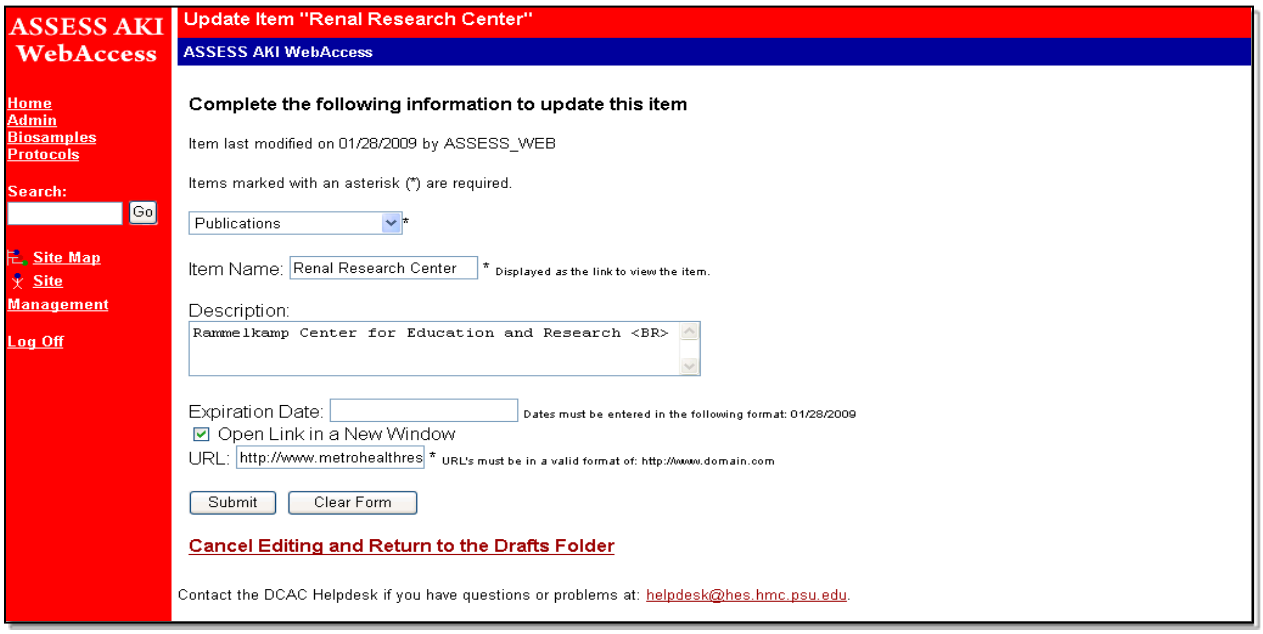


- If you have multiple items to post, select the link to 'Add Another Item to the Folder'. Otherwise, select the link to 'Return to the Folder'.



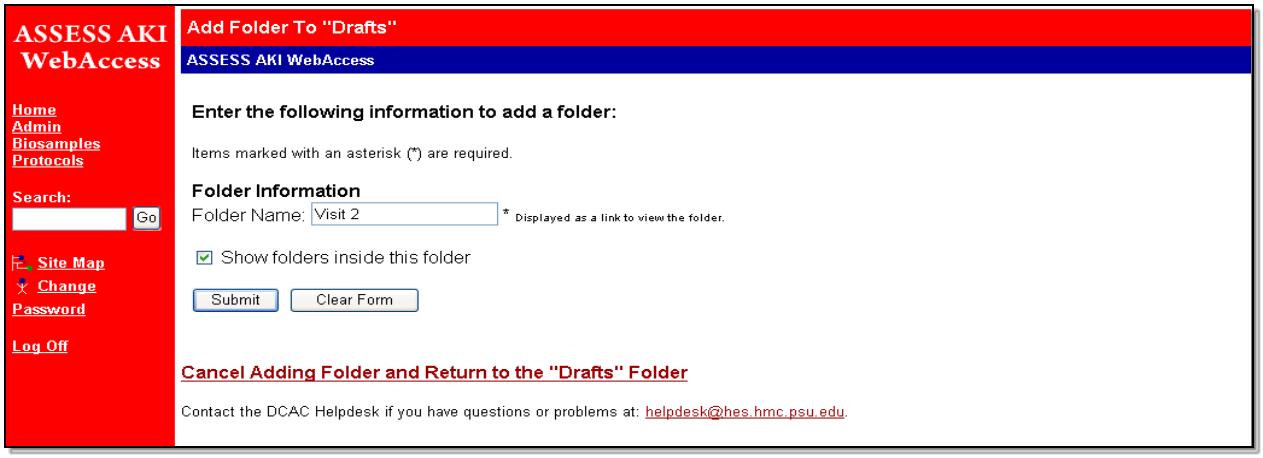
Editing a URL

- In order to change the information within a URL item, select the icon next to the item.
- Modify any of the following: Category, Item Name, Description, Expiration Date, Open in new window, and/or URL. (Optional)
- Select the 'Submit' button.

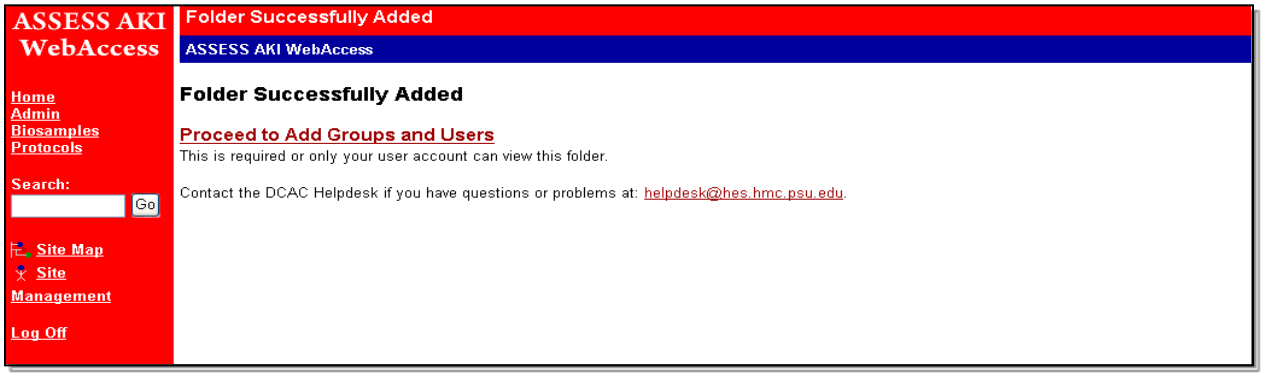


9.E.2.d Adding a Folder

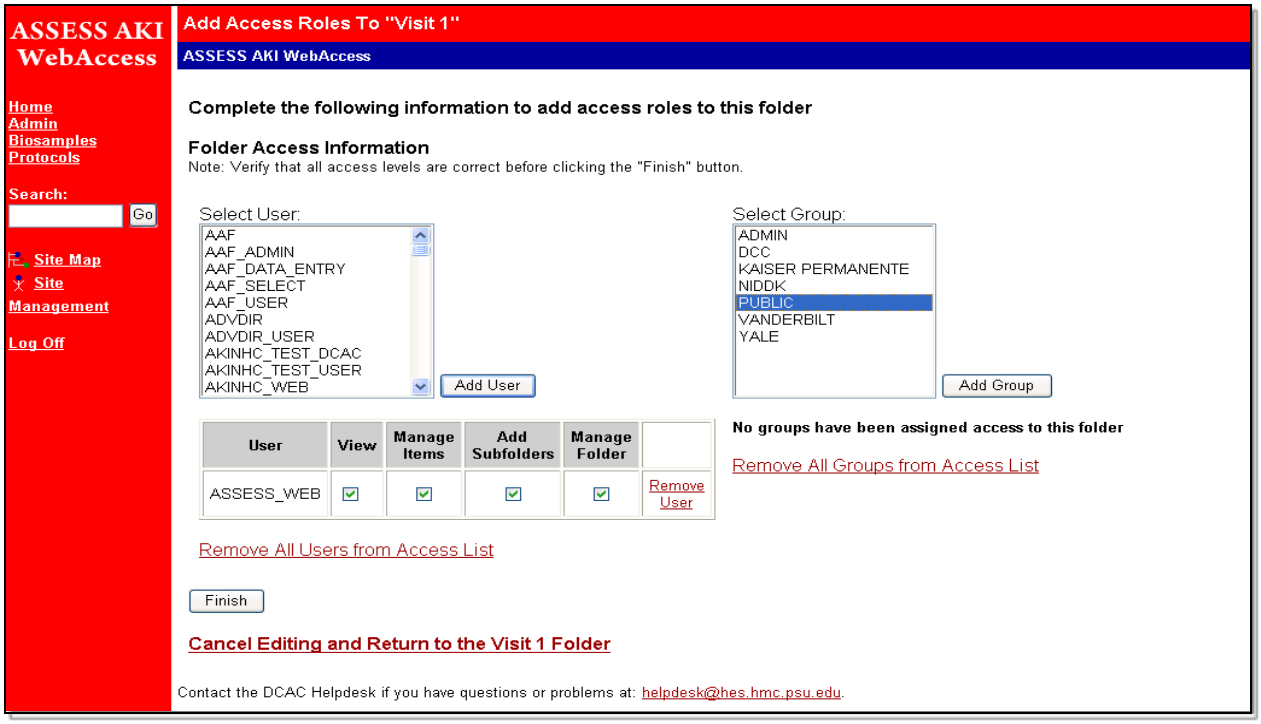
- To create a new folder in the website, navigate to the folder in which you want to create the new folder. Select the Edit button on the top right corner of the website. Select the 'Add Folder' button.
- Provide the Folder name. (Required)
- The 'Show folders inside this folder' checkbox allows the new folder to have subfolders (if a user chooses to create them). Turning off the checkbox will prevent the new folder from having subfolders.
- Select the 'Submit' button.



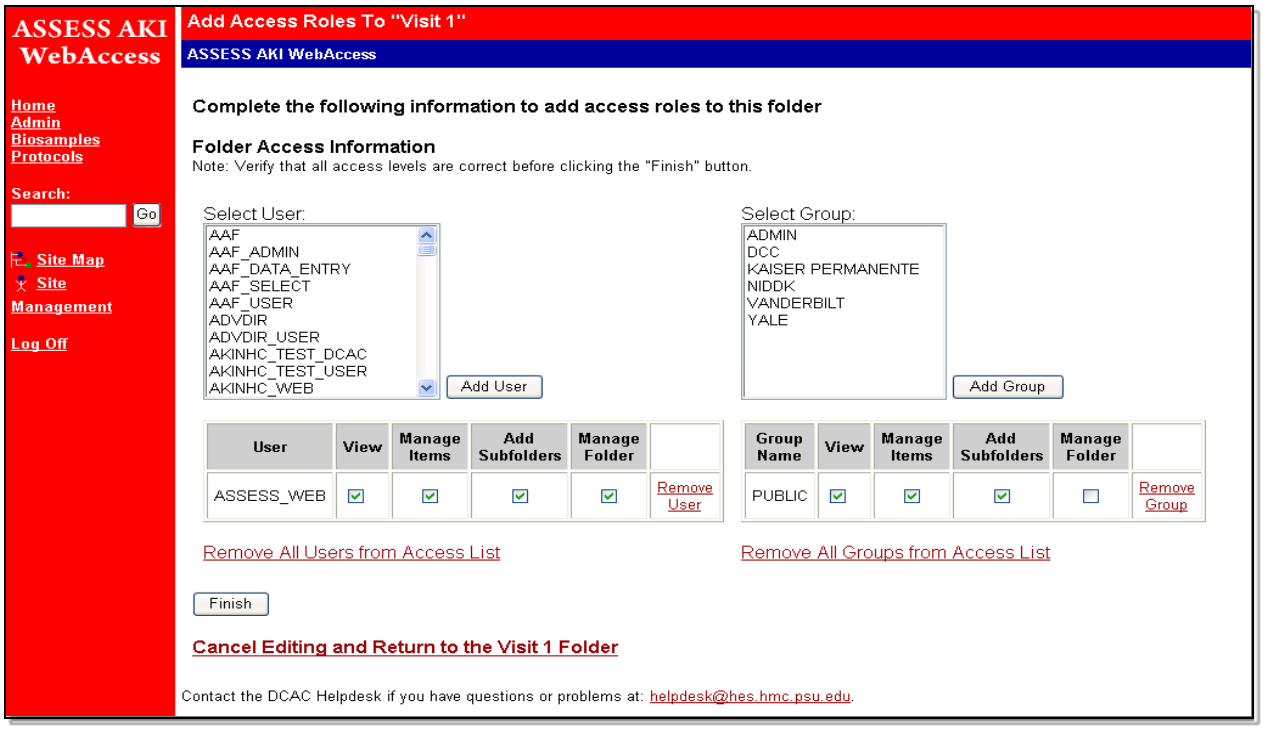
- Select the Proceed to Add Groups and Users link.



- Determine which groups should have access to the new folder. Groups are descriptively named to indicate the users who belong to the group. The Public group will contain all users on the ASSESS AKI website. Highlight the group(s) to add and select the 'Add Group' button. If you do not see the group that you are looking for, please contact the ASSESS AKI helpdesk.



- Adding a group will allow you to select what type of permissions to give the group. Select View, Manage Items, and Add Subfolders.
- Select the 'Finish' button.



10 STUDY SITE DATA ENTRY APPLICATION

10.A Application Main Menu

The application consists of two main menu types: 1) the study main menu and 2) the protocol main menu. The study main menu (see Figure 10-1) allows access to a limited group of application modules. These are modules that do not require the user to be logged into any particular protocol and apply to all protocols study-wide. There will only ever be one study main menu.

The second type of menu, the protocol main menu (see Figures 10-2), is where the user should go to perform protocol-specific actions such as enrolling a participant into a protocol. Depending on the number of protocols, there will be multiple protocol main menus that are all accessible from the study main menu. For ease of use, the modules available on the study main menu are also available from within each protocol main menu.

Because there are different requirements for Site and DCC users, each menu will appear different. An example of the Site menus can be seen in Figures 10-1 and 10-2.

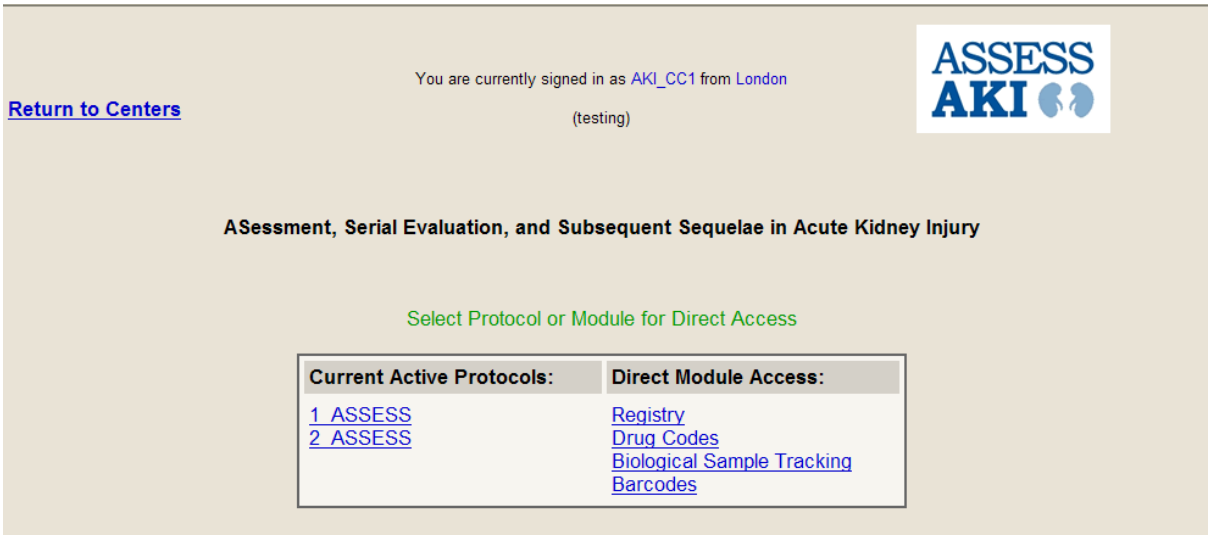


Figure 10-1

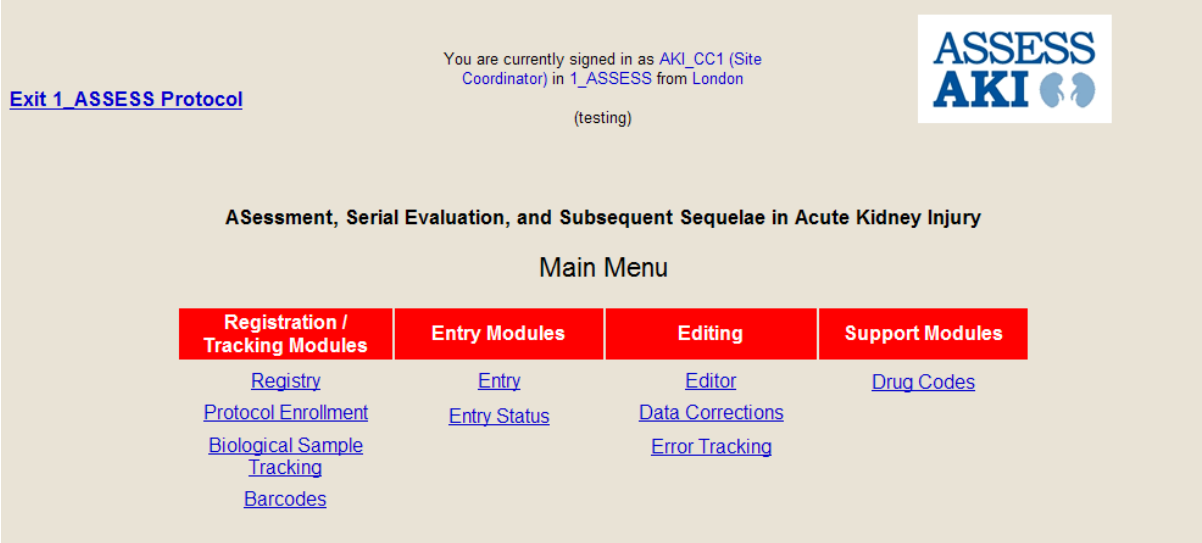


Figure 10-2

On the Site side of the application, if the user belongs to a site that has multiple centers, he or she will be directed to a Center Selection menu when logging into the application (see Figure 10-3). Upon selecting the center the user would like to enter, the user will be directed to the Main Menu. After the user enters a protocol Main Menu, they will receive the following notices if applicable:

If there are queries that require coordinator action, the user will get a prompt that states, "There are XX queries currently at Center status." Press the 'OK' button to continue. (See Figure 10-4)

- The user can view these queries in the Error Tracking module. For more information about queries, see Section 10.B.8, Error Tracking.

If there are data corrections that require coordinator action, the user will get a prompt that states, "There are XX data corrections currently at Center status." Press the 'OK' button to continue. (See Figure 10-5)

- The user can view these data corrections in the Data Corrections module. For more information about data corrections, see Section 10.B.6, Data Corrections.

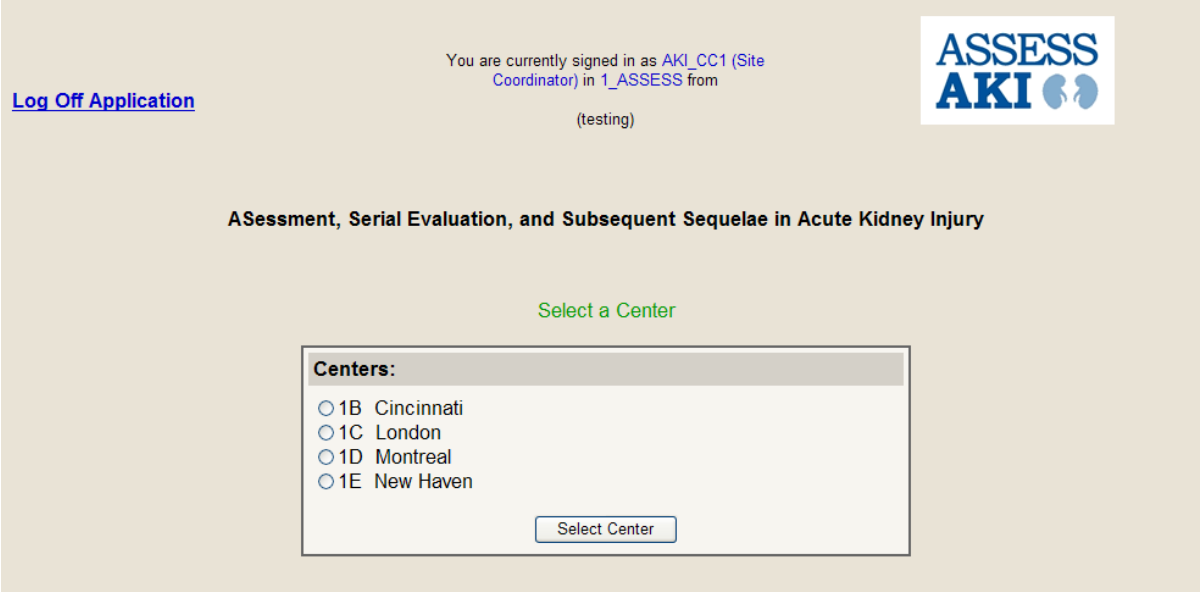


Figure 10-3

Figure 10-4

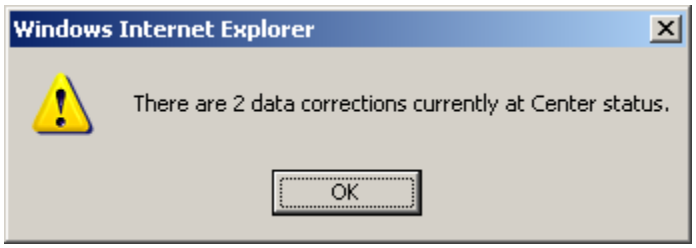


Figure 10-5

10.B Study Site Modules

At the top of each module, the information displayed will tell you: 1) what user you are logged in as, 2) what protocol you are currently working with, and 3) what study site you are logged in as. When using the application, please verify that this information is correct. If it is not, please contact the helpdesk.

10.B.1 Registry

This module allows the Site staff the ability to register a participant into a registry and assign the participant a unique Master ID. The Master ID will be used to link multiple study identification numbers across the

ASSESS AKI application. For additional information regarding the Registry module, see Section 12, Registry.

The individuals who can access this module are: Research Coordinators, Scientific Coordinators, Data Management staff.

Before adding a new participant into the Registry, the user has the option to search the database for a participant who may match any of the search criteria.

In order to search the Registry for the participant:

- Select the 'Registry' link under the Direct Module Access heading on the study Main Menu or under the Registration/Tracking Modules heading on the protocol Main Menu.
- Enter the participant's initials in the Initials field.
- Enter the participant's date of birth in the Date of Birth field.
    - Note: If you type in 8 numbers, the application will automatically include slashes (/) to follow the format MM/DD/YYYY.
- Select the appropriate option for the participant's gender.
- Press the 'Execute Query' button to complete the search.
- If a participant exists in the database that has the same initials, date of birth, or gender the data will appear beneath the Registry Search box. If this participant has already been entered into the Registry and enrolled in a protocol, you should verify the participant match using the participant assignment logs. Once the participant has been verified and the information returned matches the participant, you can proceed to Protocol Enrollment using the previously assigned Master ID. If the participant is new to the network, an extra initial will need to be added to enter the new participant into the Registry.
- If no participants meet any of the criteria you specified, the screen will display the message 'No records matched your search criteria.' At this point, you can proceed to the new registration steps below.

In the results section of the page, you will see information displayed for the following fields (see Figure 10-6): Master ID, Participant IDs, Initials, DOB, Gender, Primary Racial Category, Center, and Registry Report.

- The Master ID column will display the number that uniquely identifies the participant in the ASSESS AKI system.
- The Participant ID column will display all the Participant IDs that were registered under that Master ID. The Participant IDs will appear in order of most recent registered Participant ID to earliest registered Participant ID.
    - Note: If no Participant ID appears, this means that this person was entered into the registry but has not yet participated in any ASSESS AKI studies.
- The Initials column will display the initials given at the participant registration.
- The DOB column will display the date of birth given at the participant registration.
- The Gender column will display the gender given at the participant registration.

- The Primary Racial Category will display the racial background given at the participant registration.
- The Center column will display the study site that performed the participant's registration.
- The Registry Report column will display a link to print the participant's Registry Data Summary.

Below the Search Results is a 'Register New Participant' link. This link can be used to register a new participant if the search results confirm that this is a new participant who has not already been registered in ASSESS AKI.

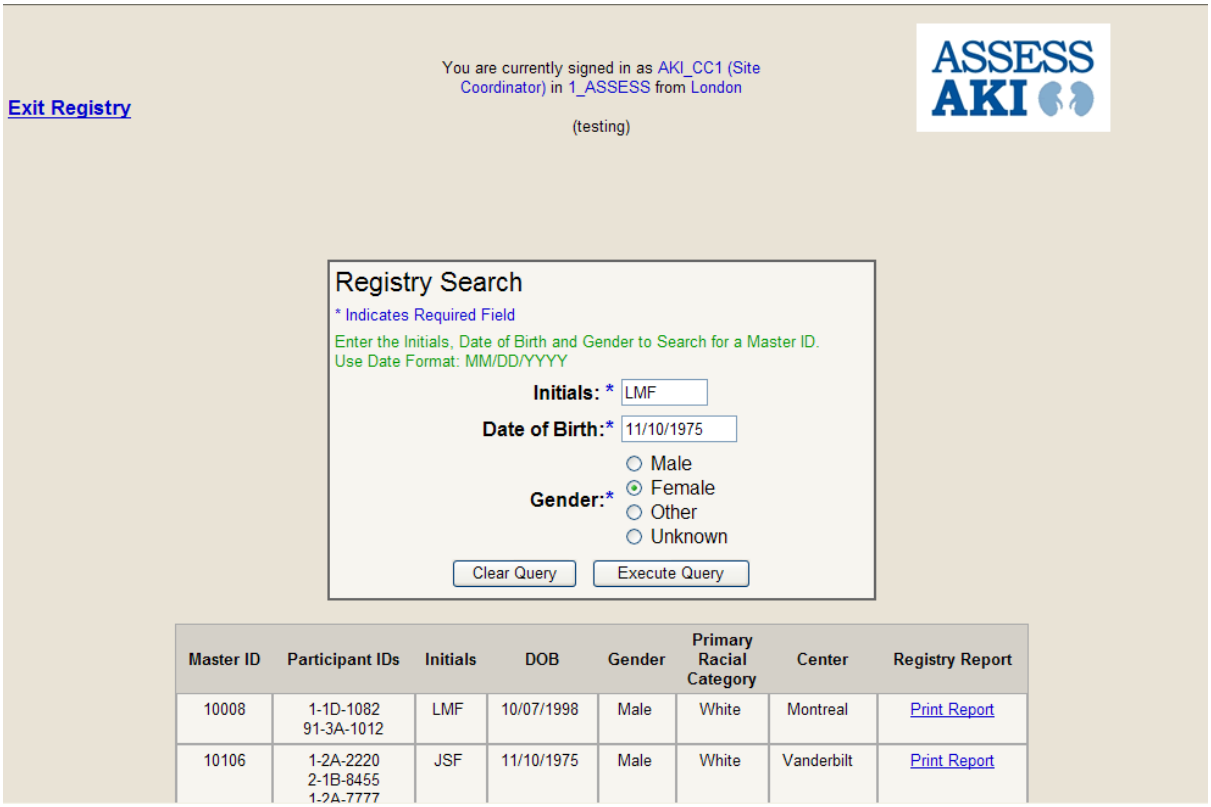


Figure 10-6

In order to register a new participant:

- Perform the above steps to search the Registry for that participant.
- Click the 'Register New Participant' link.
- The Registry First Entry screen (see Figure 10-7) will be displayed on the following screen.
- Enter the participant's initials in the Initials field.
- Enter the Coordinator ID in the Coordinator ID field.
- Enter the value for whether the participant is 18 - 89 in the Participant 18 - 89 (1000) field.
- Enter the participant consent value in the Participant Consent (1010) field.
- Enter the date the consent was given in the Date Participant Consent (1020) field.

  - Note: If you type in 8 numbers, the application will automatically include slashes (/) to follow the format MM/DD/YYYY.
- Enter the surrogate consent value in the Surrogate Consent (1030) field.
- Enter the date the surrogate consent was given in the Date Surrogate Consent (1040) field.
  - Note: If you type in 8 numbers, the application will automatically include slashes (/) to follow the format MM/DD/YYYY.
- Enter the parent/guardian consent value in the Parent/Guardian Consent (1050) field.
- Enter the date the parent/guardian consent was given in the Date Parent/Guardian Consent (1060) field.
  - Note: If you type in 8 numbers, the application will automatically include slashes (/) to follow the format MM/DD/YYYY.
- Enter the participant assent value in the Participant Assent (1070) field.
- Enter the date the participant assent was given in the Date Participant Assent (1080) field.
  - Note: If you type in 8 numbers, the application will automatically include slashes (/) to follow the format MM/DD/YYYY.
- Enter the participant's date of birth in the Date of Birth (1090) field.
  - Note: If you type in 8 numbers, the application will automatically include slashes (/) to follow the format MM/DD/YYYY.
- Enter the value for the participant's gender in the Gender (1100) field.
- Enter the participant's American Indian or Alaskan Native racial status in the American Indian or Alaskan Native (1110) field.
- Enter the participant's Asian racial status in the Asian (1120) field.
- Enter the participant's Black or African American racial status in the Black or African American (1130) field.
- Enter the participant's White racial status in the White (1140) field.
- Enter the participant's Native Hawaiian or Other Pacific Islander racial status in the Native Hawaiian or Other Pacific Islander (1150) field.
- Enter the participant's other racial status in the Other (1160) field.
- Enter the participant's primary racial category value in the Primary Racial Category (1170) field.
- Enter the value for the participant's ethnic background in the Ethnic Background (1180) field.
- Press the 'Save' button.
  - Note: The data entered (Date of Birth, Initials, and Gender) will be compared against the database and if all these values are the same as the data for another Master ID already assigned, you will receive an error. At this point, you should cancel out of the registry to re-query or contact the DCC for further assistance.

- A Registry Second Entry screen will be displayed in which you should enter the same data again.
- Press the 'Save' button.
- If there are discrepancies between the data entered in First Entry and the data entered in Second Entry, a Registry Data Entry Discrepancies screen will be displayed (see Figure 10-8) to aid in correcting the data.
- If the value entered during first entry is correct, click the radio button located under the heading First Entry. If the value entered during second entry is correct, click the radio button located under the heading Second Entry. If neither value is correct, click the radio button located under the heading Other and provide a valid value in the blank.
- Once the discrepancies have all been fixed, press the 'Save' button.
    - Note: The data entered (Date of Birth, Initials, and Gender) will be compared against the database and if all these values are the same as the data for another Master ID already assigned, you will receive an error. At this point, you should cancel out of the registry to re-query or contact the DCC for further assistance.
- If there were no discrepancies, or after the discrepancies have been corrected, the Registry Data Summary screen (see Figure 10-9) will be displayed.

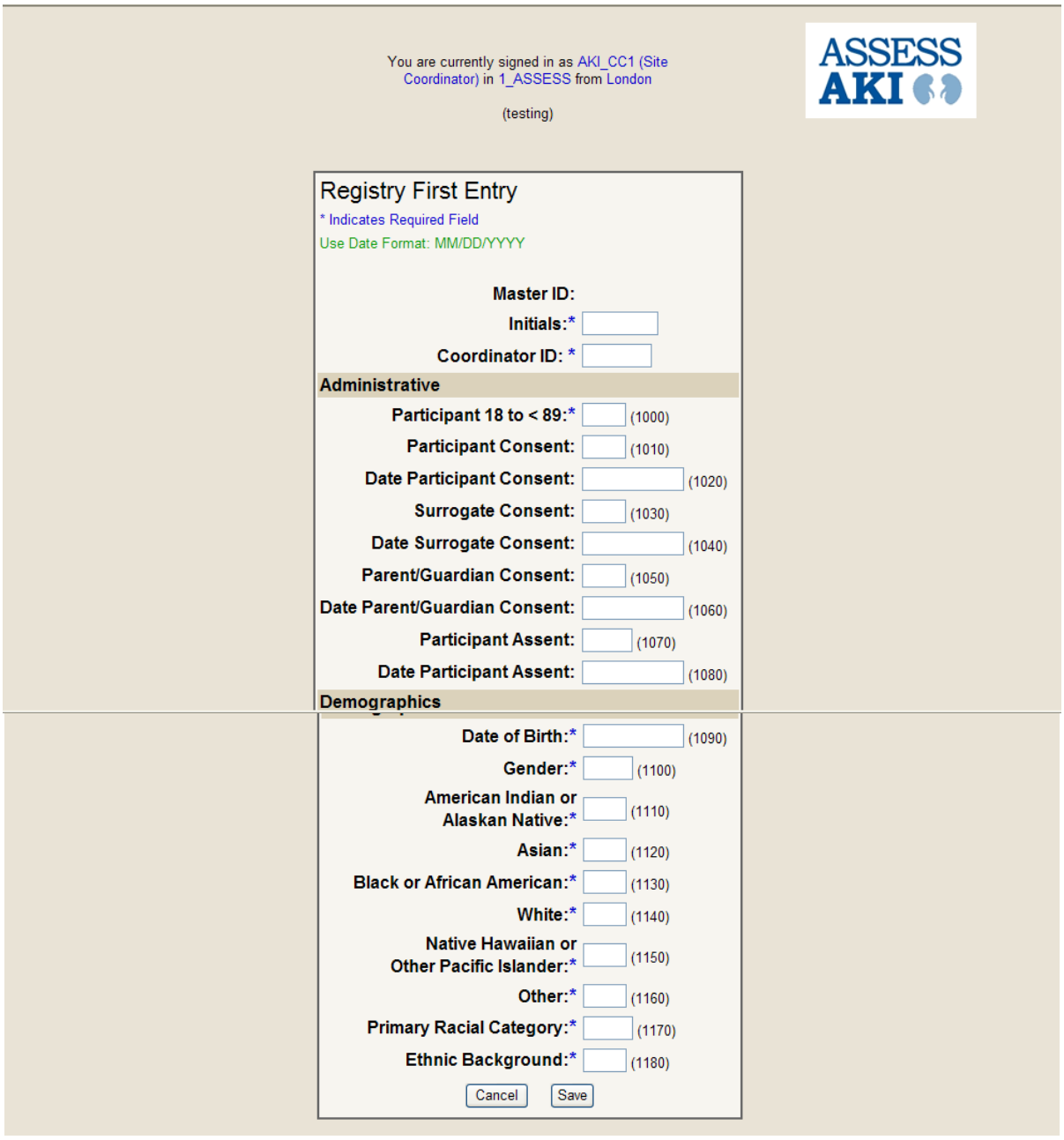

You are currently signed in as AKI_CC1 (Site Coordinator) in 1_ASSESS from London
(testing)
ASSESS AKI
Registry First Entry
* Indicates Required Field
Use Date Format: MM/DD/YYYY
Master ID:
Initials:*
Coordinator ID: *
Administrative
Participant 18 to < 89:* (1000)
Participant Consent: (1010)
Date Participant Consent: (1020)
Surrogate Consent: (1030)
Date Surrogate Consent: (1040)
Parent/Guardian Consent: (1050)
Date Parent/Guardian Consent: (1060)
Participant Assent: (1070)
Date Participant Assent: (1080)
Demographics
Date of Birth:* (1090)
Gender:* (1100)
American Indian or Alaskan Native:* (1110)
Asian:* (1120)
Black or African American:* (1130)
White:* (1140)
Native Hawaiian or Other Pacific Islander:* (1150)
Other:* (1160)
Primary Racial Category:* (1170)
Ethnic Background:* (1180)
Cancel
Save

Figure 10-7

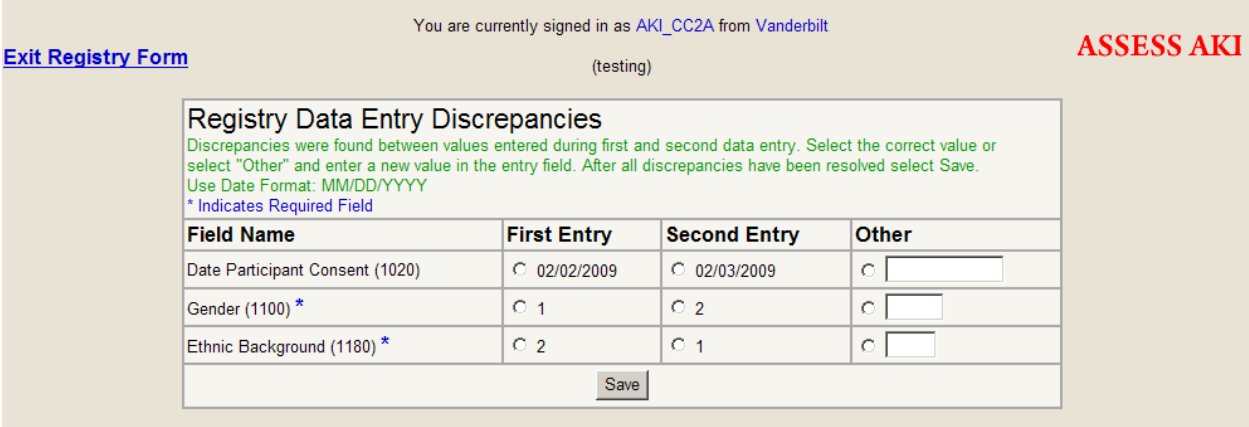


Figure 10-8

Figure 10-9

Once a participant's information has been successfully entered into the registry, registry status is Complete.

10.B.2 Protocol Enrollment

The individuals who can access this module are: Research Coordinators, and Data Managers. In order to enroll a new participant into a protocol:

- Select the 'Protocol Enrollment' link under the Registration/Tracking Modules heading on the protocol Main Menu.
- The Protocol Enrollment screen (see Figure 10-10) will be displayed on the next screen.
- The following fields are required: Master ID, Initials, Date of Birth, and Participant ID.
- Enter the Master ID that was assigned to this participant through the Registry module in the Master ID field.
- Enter the participant's initials in the Initials field.
- Enter the participant's date of birth in the Date of Birth field.
    - Note: If you type in 8 numbers, the application will automatically include slashes (/) to follow the format MM/DD/YYYY.
- The Protocol Number will be populated automatically based on the Protocol the user is logged into.
- For the DCC, enter the participant's center number in the Center Number field. For Research Coordinators, the center number will be automatically populated.
- Enter the assigned four-digit participant number in the Participant ID field.
- Press the 'Save' button.
- If there were no problems enrolling the participant, the fields will clear and you will see a green message at the top of the screen that says the enrollment was performed successfully.
- If there were problems enrolling the participant, the values will remain in the fields and you will see a red message at the top of the screen that will describe the error.

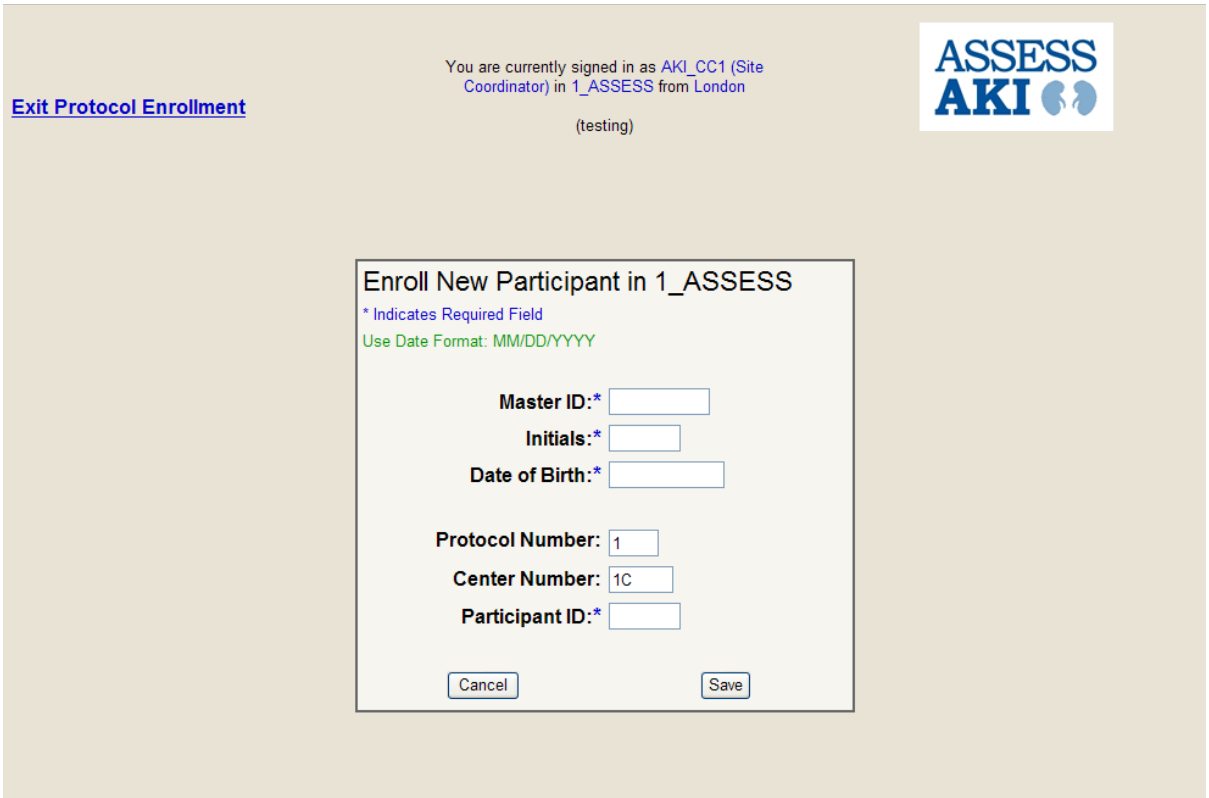


Figure 10-10

10.B.3 Entry

The individuals who can access this module are: Data Management staff and Research Coordinators.

This module allows Site personnel to input data collected on the paper forms into corresponding electronic packet or single forms and save the information to the database.

Do not use the Back button to go back in browser history during entry. If there is a question about what data was entered, the user should pull the form up in Editor mode after entry has been completed.

In order to enter a packet form:

- Select the 'Entry' link under the Entry Modules heading on the protocol Main Menu.
- The following fields are required on the setup screen (see Figure 10-11): Participant ID, Visit Number, and Entry Type.
- Enter a valid participant ID in the Participant ID field.
  - The protocol will auto-populate based on the protocol the user is currently logged into.
  - The center number will auto-populate based on the user who is currently logged on.
  - Note: If the participant has not been enrolled in this protocol, you will receive a pop-up message that says "The participant ID has not been enrolled in this protocol." Once you press the 'OK' button, the participant ID and initials field will be cleared out and the cursor will move back to the participant ID field.
- The Initials field will populate once the entire Participant ID field has been completed.

- Select a valid visit number from the Visit Number drop-down box.
  - Based on what data is already entered for this participant, the visit number should be the next available visit number or a non-sequential visit number.
- Select Packet from the Entry Type drop-down box.
- The Form Name and Visit Date fields will be inactive.
- Click the 'Packet Missing' button if there is no paper form completed for this participant on this visit date.
  - You will be prompted with a message that says, "This will mark the visit packet permanently missing. Press OK to continue." If you want to proceed with the action, press the 'OK' button. Otherwise, press the 'Cancel' button.
  - If the packet is required, the 'Packet Missing' button will be disabled.
- If the packet is not missing, click the 'Proceed' button to start entering packet form data.
  - You will be prompted with a message to make sure you are ready to enter data for the participant at the visit you specified. If you want to proceed with the action, press the 'OK' button. Otherwise, press the 'Cancel' button.
  - If the same packet has been entered for this participant, you will receive a message that says, "This packet has already been entered."
  - Enter the data collection (CRF) form information into the corresponding electronic form fields. To proceed to the next electronic form field, simply press the 'Enter' key. You can also click on the electronic field.
  - If the form is not a required form, it will have a Form Missing button that can be pressed to leave all the fields blank and move on to the next data entry form. If the form is required, the Form Missing button will not be displayed on the form.
  - If the form is a repeating type form, there will be a 'Save/Next Record' button which can be used to save the current row being entered and enter a new row. After all rows have been entered, the 'Save' button can be pressed to save the entire form with all entered rows.
- Press the 'Cancel' button to clear the setup form and change the field information.
- When the last form (packet or tracking form) in a packet has been saved the user will be prompted that entry is complete for the packet.

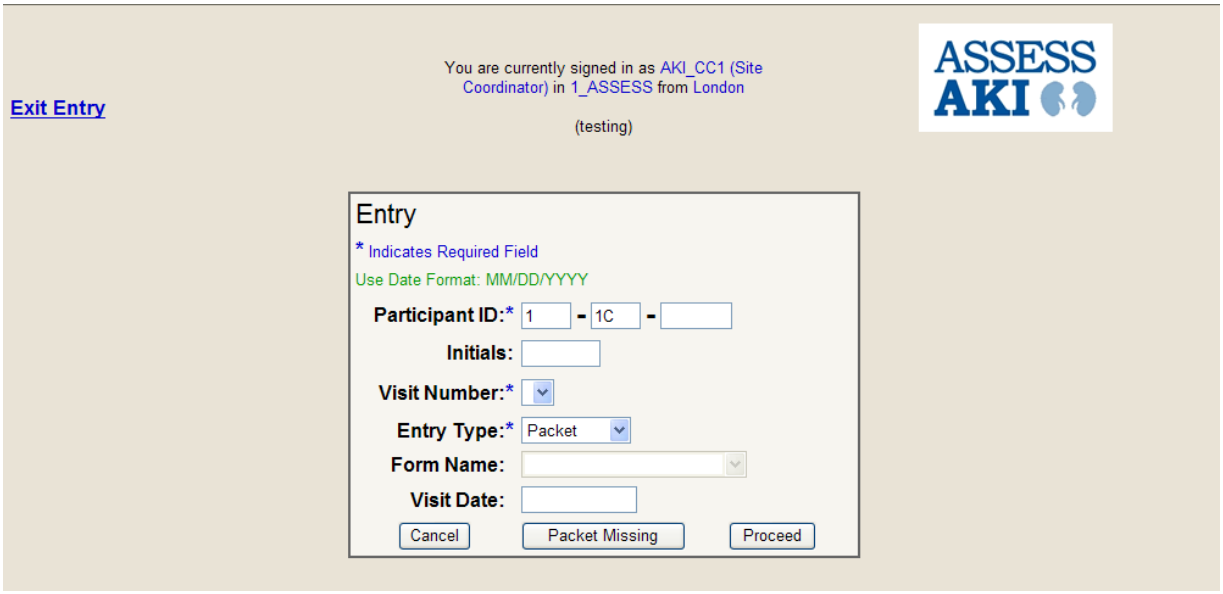


Figure 10-11

In order to enter a single form:

- Select the 'Entry' link under the Entry Modules heading on the protocol Main Menu.
- The following fields are required on the setup screen: Participant ID, Visit Number, and Entry Type.
- Enter a valid participant ID in the Participant ID field.
  - The protocol will auto-populate based on the protocol the user is currently logged into.
  - The center number will auto-populate based on the user who is currently logged on.
  - Note: If the participant has not been enrolled in this protocol, you will receive a pop-up message that says "The participant ID has not been enrolled in this protocol." Once you press the 'OK' button, the participant ID and initials field will be cleared out and the cursor will move back to the participant ID field.
- The Initials field will populate once the entire Participant ID field has been completed.
- Select a valid visit number from the Visit Number drop-down box.
  - Single forms can be entered for any previously entered visit, the first non-entered sequential visit or any non-sequential visit.
- Select Single from the Entry Type drop-down box.
- Choose the form name by clicking the down arrow and selecting a form from the displayed drop-down box.
  - You cannot type into the Form Name field on the query screen. That field will auto-populate with the value you choose in the drop-down.
  - You cannot choose more than one form from the drop-down.

- Enter a valid visit date in the Visit Date field.
  - The date entered must be between the protocol start date and the current date.
- Click the 'Proceed' button to start entering single form data.
  - You will be prompted with a message to make sure you are ready to enter data for the participant at the visit you specified. If you want to proceed with the action, press the 'OK' button. Otherwise, press the 'Cancel' button.
  - If the same form has been entered for this participant on the same date, you will receive a message that says, "This form has already been entered."
  - Enter paper form information into the corresponding electronic form fields.

Press the 'Cancel' button to clear the setup form and change the field information.

After the last form in the visit packet is saved or when the single form is saved, the Entry Errors Report (see Figure 10-12) will be displayed showing all errors that have been made during entry.

ASSESS AKI - Entry Errors

Current as of: 07/22/2009

Participant: 1-2A-1001
Visit: 0

Form: ELIG1A
Form Type: P
Visit Date: 01/01/2009

Record ID	Error	Field	Original Value	Correct Value	Error Message
-	3.001	elg1a_1160	0	_____	Q1160 on the ELIG1A form indicates the subject is ineligible, however Q1010 on the WITHDR form indicates otherwise
-	3.501	elg1a	07/01/2009	_____	ELIG1A form is completed, however the participant is enrolled in the wrong protocol, please contact the DCC

Figure 10-12

In order to enter a concurrent form:

- Select the 'Entry' link under the Entry Modules heading on the protocol Main Menu.
- The following fields are required on the setup screen: Participant ID, Visit Number, Entry Type and Form Name.
- Enter a valid participant ID in the Participant ID field.
  - The protocol will auto-populate based on the protocol the user is currently logged into.

  - The center number will auto-populate based on the user who is currently logged on.
  - Note: If the participant has not been enrolled in this protocol, you will receive a pop-up message that says "The participant ID has not been enrolled in this protocol." Once you press the 'OK' button, the participant ID and Initials field will be cleared out and the cursor will move back to the participant ID field.
  - The Initials field will populate once the entire Participant ID field has been completed.
- Select a visit number by clicking the down arrow on the Visit Number drop-down box.
- Select the form option by clicking the down arrow and choosing Concurrent from the Entry Type drop-down box.
- Select the form you will be entering by clicking the down arrow on the Form Name drop-down box.
- The Visit Date field will be disabled and should not allow any values to be typed in by the user.
- Select the 'Proceed' button to start entering concurrent form data.
  - You will be prompted with a message to make sure you are ready to enter data for the participant at the visit you specified. If you want to proceed with the action, press the 'OK' button. Otherwise press the 'Cancel' button.
- Select the 'Cancel' button to clear the setup form and change the field information.
- Enter form data into the web form.
- If the form is a repeating type form, there will be a 'Save/Next Record' button which can be used to save the current row being entered and enter a new row. After all rows have been entered, select the 'Save' button to save the entire form with all entered rows.
- After you select the 'Save' or 'Exit' button, the front end validation checks will be run on the data entered.
  - If there are errors as a result of the validation, the Entry Errors Report (see Figure 10-13) will be displayed showing all errors that have been made during entry.
  - All errors for the concurrent form will appear in addition to any 3 checks for any visit packet.
  - An Ongoing Records Report (see Figure 10-14) will be displayed showing the records that have been entered and marked as ongoing on the concurrent form.

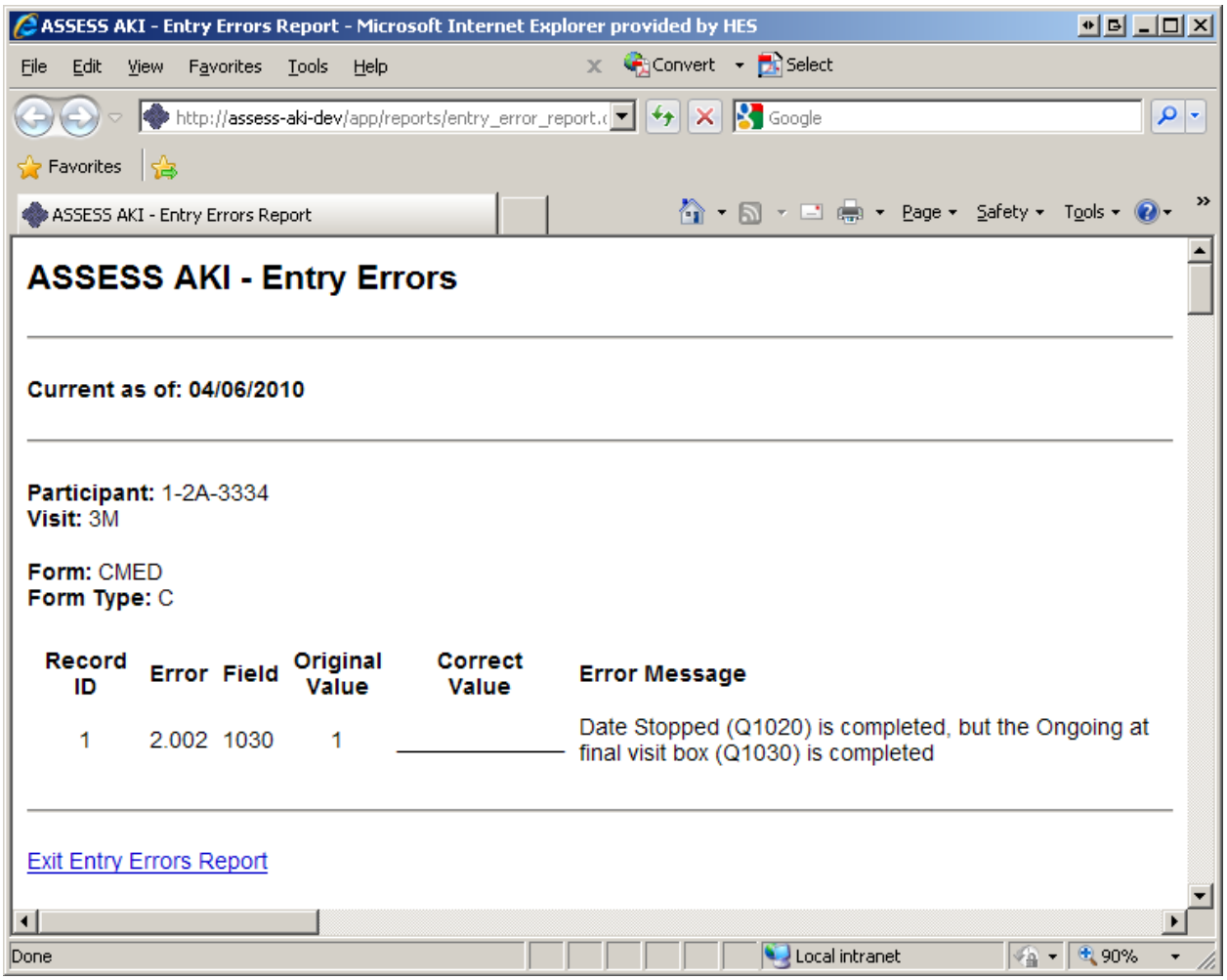

ASSESS AKI - Entry Errors Report - Microsoft Internet Explorer provided by HES
File Edit View Favorites Tools Help
Convert
Select
http://assess-aki-dev/app/reports/entry_error_report.
Google
Favorites
ASSESS AKI - Entry Errors Report
Page
Safety
Tools
ASSESS AKI - Entry Errors
Current as of: 04/06/2010
Participant: 1-2A-3334
Visit: 3M
Form: CMED
Form Type: C
Record ID
Error
Field
Original Value
Correct Value
Error Message
1
2.002
1030
1
Date Stopped (Q1020) is completed, but the Ongoing at final visit box (Q1030) is completed
Exit Entry Errors Report
Done
Local intranet
90%

Figure 10-13

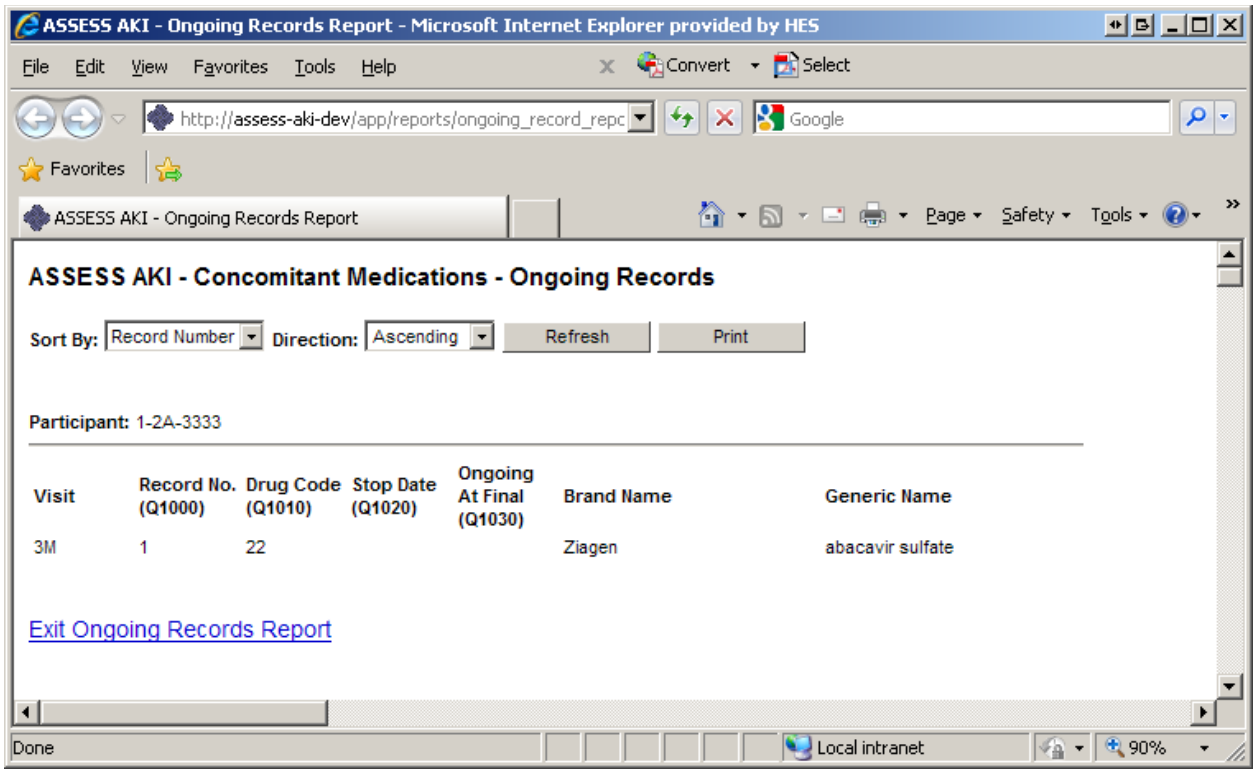


Figure 10-14

10.B.4 Entry Status

The individuals who can access this module are: Data Management staff, Research Coordinators, and Scientific Coordinators.

This module allows Center and DCC personnel to view information about participants and forms entered into the database. The user should have the ability to view participant numbers only or view the status of participant specific packets with entry information and current data in the database.

The first screen (see Figure 10-15) will allow you to enter a variety of criteria. The criteria are: Participant (including protocol number, center number and participant number), Form Name, and the type of search being performed.

- The protocol number will be pre-populated with the protocol that the user is currently logged into.
- All of the search criteria options on this screen, with the exception of the search type, are optional.
- The form name criterion is only applicable to the Forms search type.

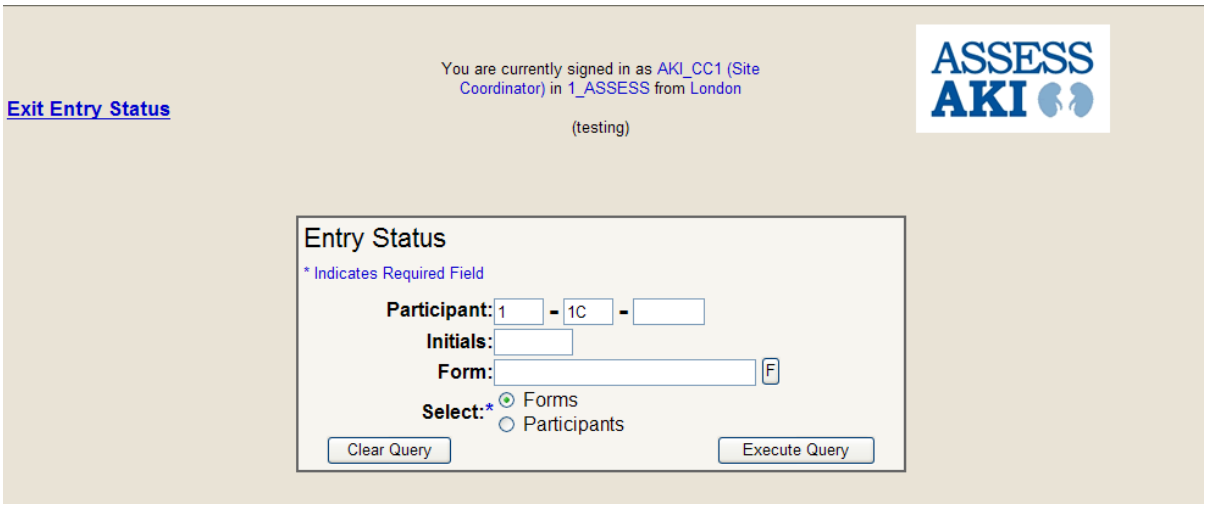
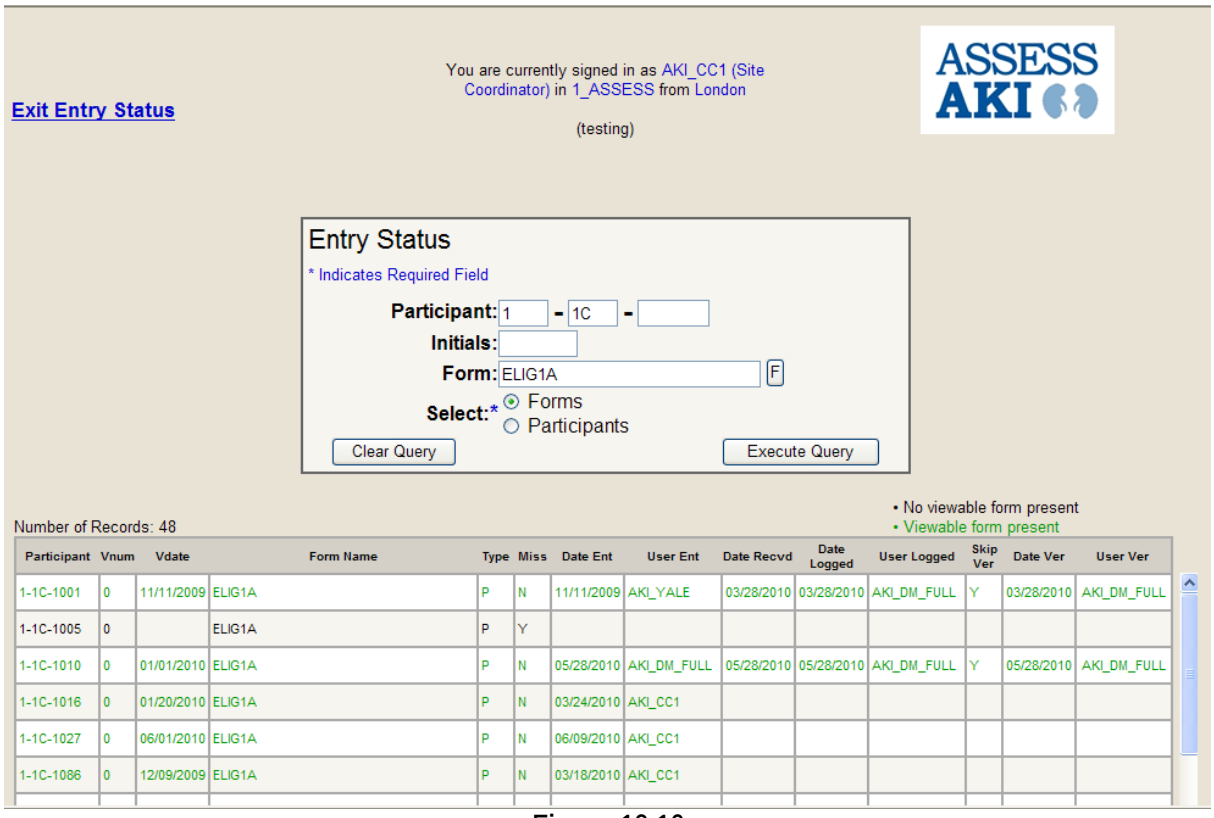


Figure 10-15

- In order to determine which forms have been entered:
- Select the 'Entry Status' link under the Entry Modules heading on the protocol Main Menu.
- If you would like to see information specific to a particular participant, enter the values in the Participant field. If a full participant ID has been entered, the Initials field will auto-populate.
- If you would like to limit your search to a particular form, click the 'F' button and select a form from the displayed drop-down list.
    - Note: In order to clear out the selected form, click on the 'F' button and click the 'Cancel' button. This should return you to the query screen and the Form field will be blank.
- Click the 'Execute Query' button.
- The results of your search will be displayed below the search area of the screen (see Figure 10-16). The information displayed is: Participant ID (Participant), Visit Number (Vnum), Visit Date (Vdate), Form Name, Form Type (Type), Form Missing Status (Miss), Date Entered (Date Ent), User Entered (User Ent), Date Received (Date Recvd), Date Logged, User Logged, Missing Verification Status (Skip Ver), Date Verified (Date Ver), and User Verified (User Ver) .
- If a form was not marked missing and if the form is either type 'S' (single) or type 'P' (packet) the row will be displayed in green text. This means that you are able to click on the form name and view the data entered for this form.
    - Note: If the form has a completed Date Ver and User Ver value, this means that the form has been verified. In this case, the data displayed by clicking on the form name will reflect what was entered during second entry, not first entry.



Participant	Vnum	Vdate	Form Name	Type	Miss	Date Ent	User Ent	Date Recvd	Date Logged	User Logged	Skip Ver	Date Ver	User Ver
1-1C-1001	0	11/11/2009	ELIG1A	P	N	11/11/2009	AKI_YALE	03/28/2010	03/28/2010	AKI_DM_FULL	Y	03/28/2010	AKI_DM_FULL
1-1C-1005	0		ELIG1A	P	Y								
1-1C-1010	0	01/01/2010	ELIG1A	P	N	05/28/2010	AKI_DM_FULL	05/28/2010	05/28/2010	AKI_DM_FULL	Y	05/28/2010	AKI_DM_FULL
1-1C-1016	0	01/20/2010	ELIG1A	P	N	03/24/2010	AKI_CC1						
1-1C-1027	0	06/01/2010	ELIG1A	P	N	06/09/2010	AKI_CC1						
1-1C-1086	0	12/09/2009	ELIG1A	P	N	03/18/2010	AKI_CC1						

Figure 10-16

In order to determine the status of participants entered into the database:

- If you would like to see participant information specific to a particular site, select the Participants radio button.
- Click the 'Execute Query' button.
- The results of your search will be displayed below the search area of the screen (see Figure 10-17). The information displayed is: Participant ID (Participant), Initials (Init), Date Enrolled, User Enrolled, and Master ID.

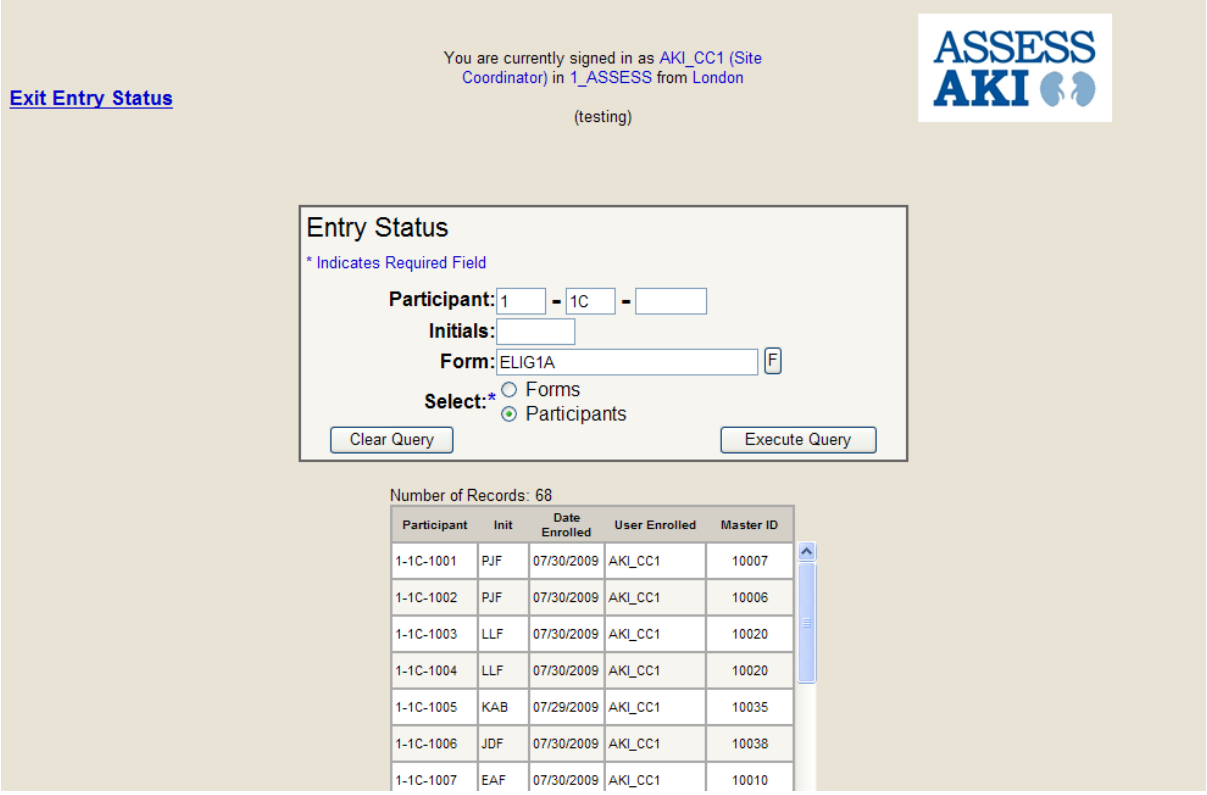


Figure 10-17

10.B.5 Biological Sample Tracking

The individuals who may access this module are: Data Management staff, Lab staff, Research Coordinators, and Scientific Coordinators.

This module facilitates the tracking process of multiple types of biological samples to multiple sites. The tracking module allows the clinical research center (CRC) to enter sample collection and shipment data for any samples collected at a visit for shipment to the Central Lab and Biorepository. The CRC creates shipment reports and export data files to accompany the samples to the Central Lab and Biorepository. The Central Lab or DCC personnel will mark the sample shipment receipt. The Central Lab and Biorepository will also have the option to send those samples on to another lab for further processing.

Enter the Biological Sample Tracking module by selecting the 'Biological Sample Tracking' link under the Direct Module Access heading on the ASSESS-AKI Main Menu or under the Registration/Tracking Modules heading on the protocol Main Menu. **Note:** If the module is accessed through the protocol main menu, the user will be limited to viewing/editing only data for the specific protocol.

The Biological Sample Tracking Menu (see Figure 10-18) will be displayed on the next screen. The actions that may be performed on this screen are: Enter/Update/Search Sample Tracking, Build a Shipment, View Shipments – Mark as Shipped/Print Logs.

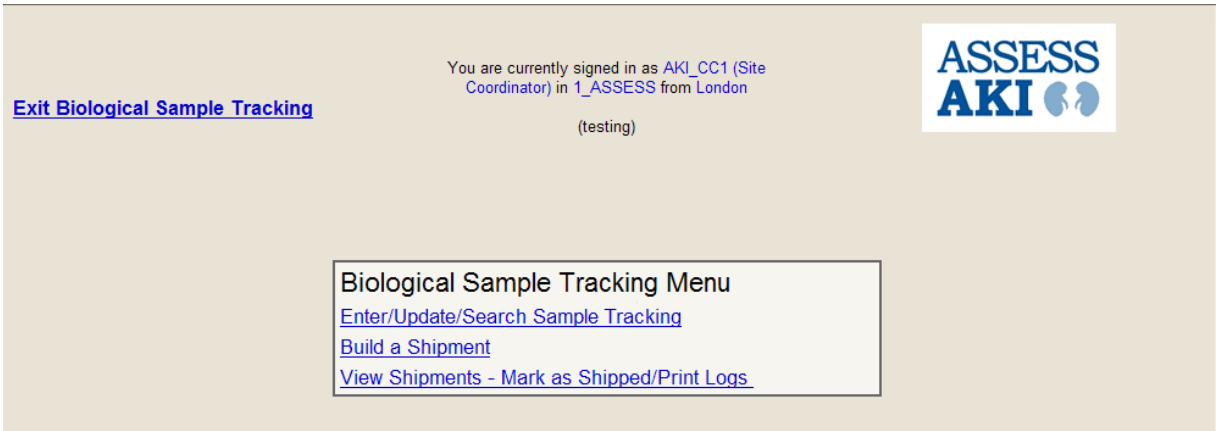


Figure 10-18

To insert new samples into biological sample tracking:

- Select the 'Enter/Update/Search Sample Tracking' link on the Biological Sample Tracking Menu.
- The Enter/Update/Search Sample Tracking screen (see Figure 10-19) will be displayed on the screen.

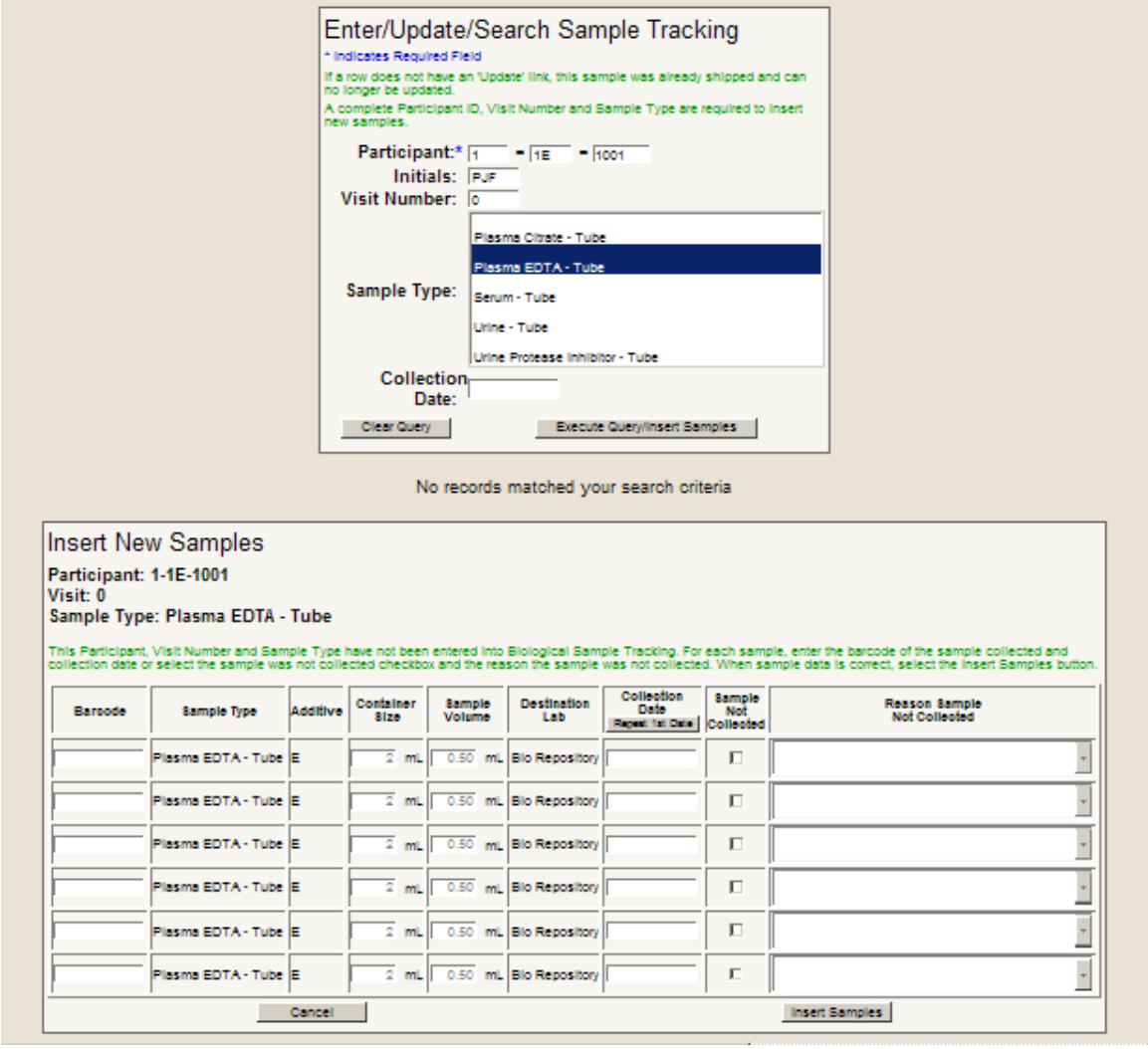


Figure 10-19

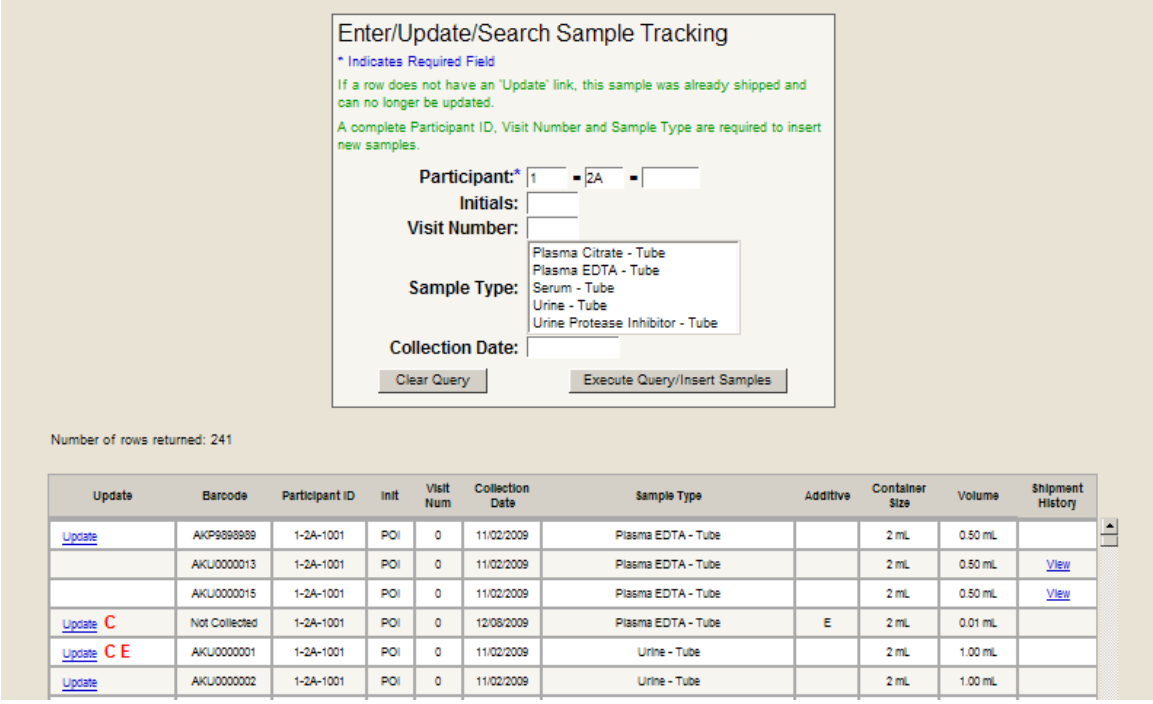
- In order to add a new sample, a complete Participant ID, Visit Number, and Sample Type must be entered.
  - If you entered the Sample Tracking screens by way of the Direct Module Access heading on the ASSESS-AKI Main Menu screen, you will be required to enter a valid protocol number. If you entered through the protocol Main Menu, the protocol number will be displayed automatically.
- If an enrolled Participant ID has been entered, the Initials field will auto-populate.
- If a Collection Date is entered, the Date will populate in the next screen.
- Select the 'Execute Query/Insert Samples' button to run your search.
- If samples were not previously entered for the participant, visit, and sample type requested, an Insert New Samples section will appear on the screen to facilitate entry of new samples.

- The Participant, Visit, and Sample Type will populate based on the data entered in the search criteria.
- A row for each sample that needs to be collected for the selected visit and sample type will be displayed.
- Enter the barcode for each sample, or choose the checkbox under 'Sample Not Collected' if the sample was not collected.
  - You may enter barcodes with a barcode scanner wand or you may type them in manually. The cursor will automatically go to the next available barcode field after a valid barcode ID is entered.
  - If the sample was not collected, select one reason under the 'Reason Sample Not Collected' drop-down box.
- Enter the Collection Date for each sample, even if it was not collected.
  - If you entered a Collection Date in the original search query, the Collection Date will be populated with that date in the Insert New Samples section.
  - If you did not enter a Collection Date in the original search query, you may enter a date for each individual sample or you may enter a date for the first sample and select the 'Repeat 1st Date' button to populate the collection date for all of the samples.
- The Container Size will be populated with a pre-defined default value. If you enter a barcode, this value will be available for edit within the pre-defined range.
- The Sample Volume will be populated with a pre-defined default value. If you enter a barcode, this value will be available for edit within the pre-defined range.
  - If the default volume does not match the volume in the scanned tube, the Sample Volume MUST be changed in the Insert New Samples section. The container volume may need to be altered to correspond to the sample volume.
    - For example, if a barcode is scanned and the default volume is recorded as 5 mL but the tube only contains 3 mL select the Sample Volume Field and update the 5.000 to 3.000.
  - The Sample Volume can never be greater than the Container Size.
- When you are done entering the required information for each sample listed, select the 'Insert Samples' button to save the data.
  - Verify the changes were saved by reviewing the samples displayed on the Entry Screen.
    - If a sample volume is incorrect, the volume should be corrected through the 'Sample Tracking Update' section of the BST.
  - You will be prompted with a message that states, 'Are you sure you want to add new samples for this participant?' If yes, select the 'OK' button. If you would like to cancel the save action and make changes to the data, select the 'Cancel' button.
  - Once the data has been saved, a 'Records saved successfully' message will be displayed in green text at the top of the screen, and the Insert Samples portion of the screen will be replaced by the search query results which will refresh and display the new samples added.

If you would like to return to the query screen without inserting any new data, select the 'Cancel' button.

To update samples for a participant:

- Select the 'Enter/Update/Search Sample Tracking' link on the Biological Sample Tracking Menu.
- The Enter/Update/Search Sample Tracking screen (see Figure 10-20) will be displayed on the screen.
- Any of the following fields may be completed to query for sample information.
  - Participant allows you to limit your search to a specific participant's samples for update.
    - If you entered the Biological Sample Tracking screens by way of the Direct Module Access heading on the ASSESS-AKI Main Menu screen, you will be required to enter a valid protocol number. If you entered through the protocol Main Menu, the protocol number will be displayed automatically.
    - Protocol Number is required; all other fields are optional.
    - To search on a participant, enter his/her entire Participant ID and if valid, the Initials will populate.
  - Visit Number allows you to limit your search to samples collected at a specific visit.
  - Sample Type allows you to limit your search to one of the samples being tracked in the system and collected at the visit (if specified).
  - Collection Date allows you to limit your search to samples collected on a particular date.
- Select the 'Execute Query/Insert Samples' button to run your search.
- In the results section of the page, you will see information displayed for the following fields (see Figure 10-20): Update, Barcode, Participant ID, Initials (Init.), Visit Number (Visit Num), Collection Date, Sample Type, Additive, Container Size, Volume, and Shipment History.



Update	Barcode	Participant ID	Init	Visit Num	Collection Date	Sample Type	Additive	Container Size	Volume	Shipment History
Update	AKP9898989	1-2A-1001	POI	0	11/02/2009	Plasma EDTA - Tube		2 mL	0.50 mL	
	AKU0000013	1-2A-1001	POI	0	11/02/2009	Plasma EDTA - Tube		2 mL	0.50 mL	View
	AKU0000015	1-2A-1001	POI	0	11/02/2009	Plasma EDTA - Tube		2 mL	0.50 mL	View
Update C	Not Collected	1-2A-1001	POI	0	12/08/2009	Plasma EDTA - Tube	E	2 mL	0.01 mL	
Update C E	AKU0000001	1-2A-1001	POI	0	11/02/2009	Urine - Tube		2 mL	1.00 mL	
Update	AKU0000002	1-2A-1001	POI	0	11/02/2009	Urine - Tube		2 mL	1.00 mL	

Figure 10-20

- The Update column will display an Update link for samples that may be updated.
  - For some samples, there may be a red 'C' or 'E' next to the Update link. The 'C' indicates that a comment has been entered by the center or the lab for this sample while the 'E' indicates that a sample was excluded from the shipment by the center or the lab.
  - If you select the C or E link, the comment or exclusion reason will appear for the user to view.
- The Barcode column will display the barcode for the sample if it was collected or the text 'Not Collected' if the sample was not collected.
- The Participant ID column will display the ID for the participant for which the sample was collected.
- The Initials column will display the participant's initials.
- The Visit Number column will display the visit at which the sample was collected.
- The Collection Date column will display the date the sample was collected.
- The Sample Type column will display the type of sample collected.
- The Additive column will display the code for the additive that was added to the sample. Additive codes are as follows:
  - C = Citrate
  - E = EDTA
  - I = Protease Inhibitor

- The Container Size column will display the size of the container in which the sample was collected.
- The Volume column will display the volume of the sample that was collected.
- The sample volume MUST represent the actual volume in the specific tube. For example a barcode is scanned and the default volume is recorded as 5 mL but the tube only contains 3 mL select the Sample Volume Field and update the 5.000 to be 3.000.
  - After making the update, select the 'Save' button and return to 'Enter/Update/Search Sample Tracking' screen.
  - Verify that the changes were saved by reviewing the samples displayed on the Entry/Update/Search screen.
- The Shipment History column will display a View link if there is shipment history to view.

- Choose the sample you would like to update and select the 'Update' link at the beginning of that row.
- The Sample Tracking Update screen (see Figure 10-21) will be displayed on the screen.

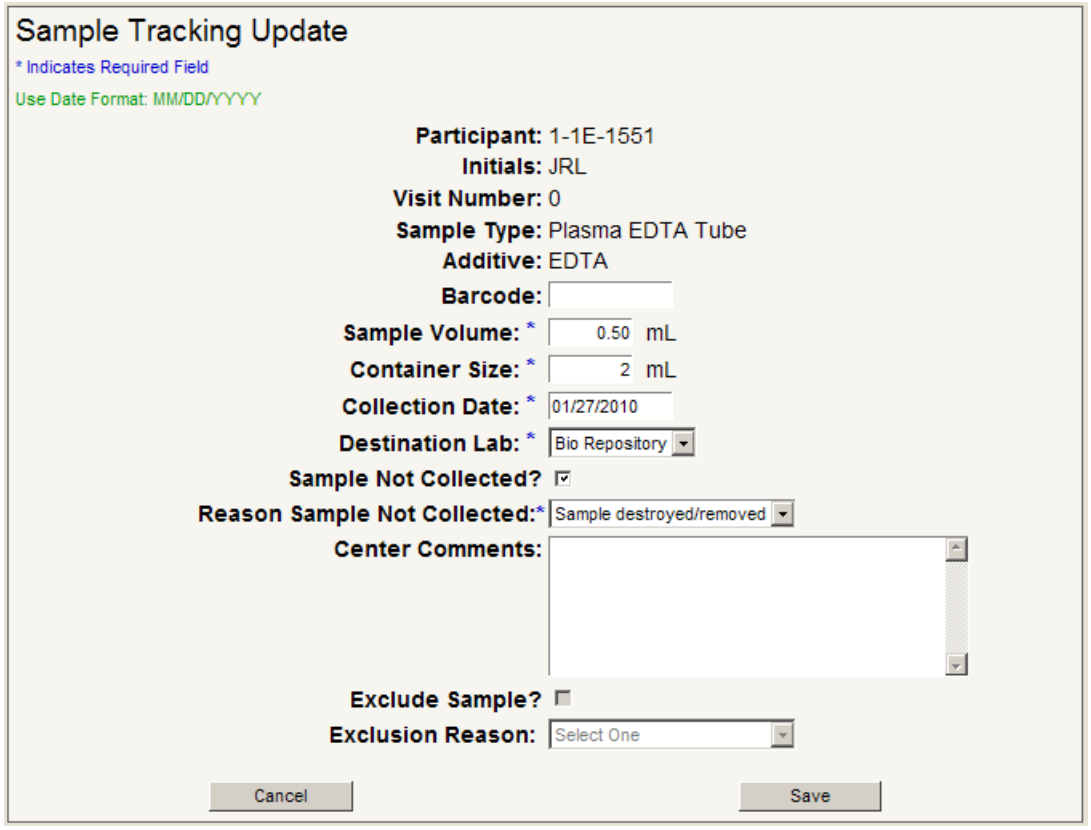


Figure 10-21

- The following fields may be updated by the center: Additive (if applicable), Barcode, Sample Volume, Container Size, Collection Date, Destination Lab (if there is more than one possibility),

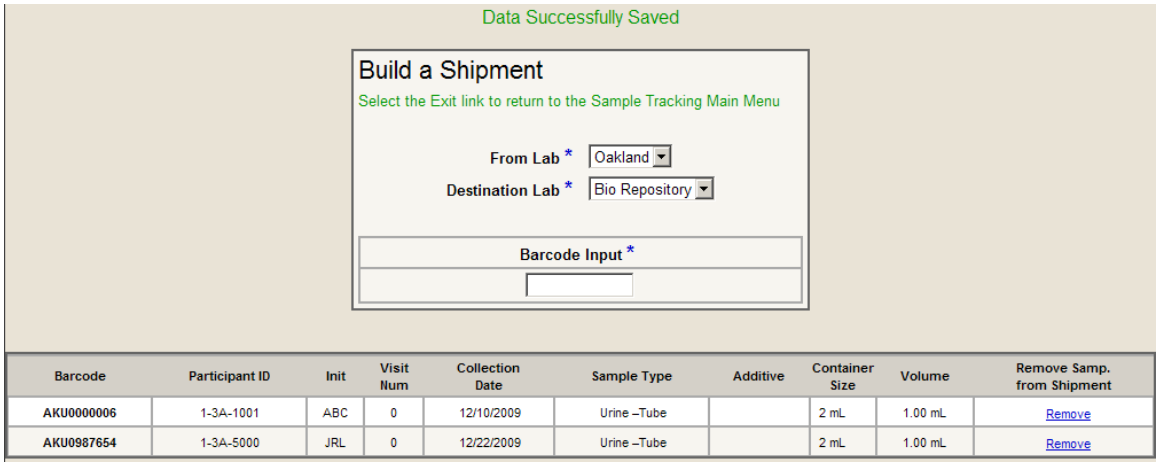
Sample Not Collected, Reason Sample Not Collected, Center Comments, Exclude Sample, and Exclusion Reason. Following is a list of restrictions to updates that may be made:

- The Additive will only be available for update if there are additives being used for the protocol, visit number, and sample type being updated.
- The Sample Volume may not exceed the Container Size.
- The Collection Date must be between the protocol start date and the current date.
- The Destination Lab drop-down box will be populated with the list of labs that are receiving samples for the protocol, visit number and type of sample being updated.
- The Reason Sample Not Collected will only be available for update if the Sample Not Collected checkbox has been checked.
- The Exclusion Reason will only be available for update if the Exclude Sample checkbox has been checked.
- The Exclude Sample checkbox will not be available for update if the sample was not collected.

- When you are finished entering the changes, select the 'Save' button.
- You will be prompted with a message that says, 'Are you sure the data are correct?' If yes and you would like to continue saving, select the 'OK' button. If you would like to make changes to what you have entered, select the 'Cancel' button.
- If you would like to leave the screen without making any changes to the data, select the 'Cancel' button.
- Once the data updates have been saved, you will receive a confirmation message at the top of the screen in green text 'Record updated successfully,' and you will be able to see the updated data in the results section of the screen.

In order to build a shipment of samples:

- Select the 'Build a Shipment' link on the Biological Sample Tracking Menu.
- The Build a Shipment screen (see Figure 10-22) will be displayed on the screen.



Barcode	Participant ID	Init	Visit Num	Collection Date	Sample Type	Additive	Container Size	Volume	Remove Samp. from Shipment
AKU0000006	1-3A-1001	ABC	0	12/10/2009	Urine –Tube		2 mL	1.00 mL	Remove
AKU0987654	1-3A-5000	JRL	0	12/22/2009	Urine –Tube		2 mL	1.00 mL	Remove

Figure 10-22

- To build a shipment, you must select a 'From Lab' and a 'Destination Lab' from the drop-down boxes.
  - The 'From Lab' will always be the center name of your institution. If you are Kaiser, all shipments will be sent from the Oakland center name.
- Enter the barcode for each sample in the Barcode Input text box.
  - You may enter barcodes with a barcode scanner wand or you may type them in manually. The cursor will automatically go to the Barcode Input field after each valid barcode ID is entered.
- If the sample has been inserted into the Biological Sample Tracking module previously and has not been sent in a previous shipment, the following sample information will be displayed on the page (see Figure 10-22): Barcode, Participant ID, Initials (Init), Visit Number (Visit Num), Collection Date, Sample Type, Additive, Container Size, Volume, and Remove Sample from Shipment link.
  - The Barcode column will display the barcode for the sample.
  - The Participant ID column will display the ID for the participant for which the sample was collected.
  - The Initials column will display the participant's initials.
  - The Visit Number column will display the visit at which the sample was collected.
  - The Collection Date column will display the date the sample was collected.
  - The Sample Type column will display the type of sample collected.
  - The Additive column will display the additive that was added to the sample.
  - The Container Size column will display the size of the container in which the sample was collected.
  - The Volume column will display the volume of the sample that was collected.
    - The sample volume MUST represent the actual volume in the specific tube.
    - Review the samples as they are scanned into the Shipment and verify that the sample volume listed in the BST matches the sample in the tube.
  - The Remove Sample from Shipment column will display a 'Remove' link to remove the sample from the shipment. Select this link if you want to remove the sample from the current shipment.
    - If a sample volume is incorrect, select the 'Remove' link which will take the sample out of the shipment 'build in progress'.
      - ✓ The volume should be corrected through the 'Sample Tracking Update' section of the BST.
      - ✓ The sample can then be added into the shipment.
- If the sample has not been inserted into the Biological Sample Tracking module previously, you will receive an alert message indicating the barcode has not been inserted into the module and asking if you want to enter it now (see Figure 10-23).

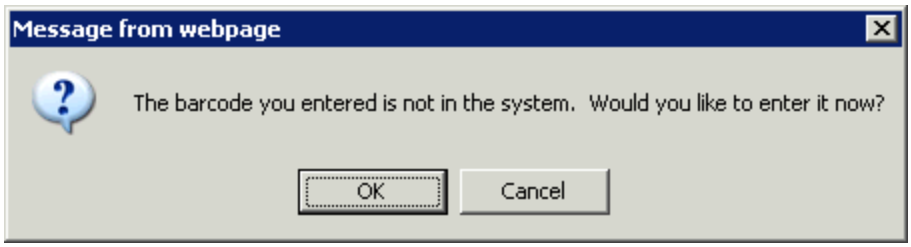


Figure 10-23

- Select 'OK' if you want to enter the sample. You will be returned to the Enter/Update/Search Sample Tracking screen to enter the sample. When you are done entering the sample, select the 'Exit Enter/Update/Search Sample Tracking' link and you will be returned to the Build a Shipment screen.
  - The previous samples that were built in the shipment will not be displayed on the screen, however they will be saved in the shipment and can be viewed in the 'View Shipments – Mark as Shipped/Print Logs' link.
- Select 'Cancel' if you do not want to enter the sample.

- Following is a list of safeguards to building a shipment:
  - You may not add a sample to the shipment if it has already been shipped.
  - You may not enter a barcode more than once.
  - You may not add a sample to a shipment if it has been excluded prior to shipping the sample.
  - You may not add a sample to a shipment going to the incorrect destination lab (i.e., V0 sample to Central Lab).
  - You cannot enter a sample to a shipment if the barcode was used at another center.
  - Centers from Cincinnati, London, Montreal, New Haven, and Vanderbilt may add samples to a shipment for participants from their own sites.
  - Kaiser may add samples to a shipment for participants from any of their three sites under the Oakland center name.
  - You may add a sample to a shipment between the 'From Lab' and 'Destination Lab' one time.
- When you are finished adding samples to the shipment, select the 'Exit Build Shipment' link.

In order to view a build in progress:

- Select the 'View Shipments – Mark as Shipped/Print Logs' link on the Biological Sample Tracking Menu.
- The Sample Tracking Shipment Area screen will be displayed on the next page (see Figure 10-24).

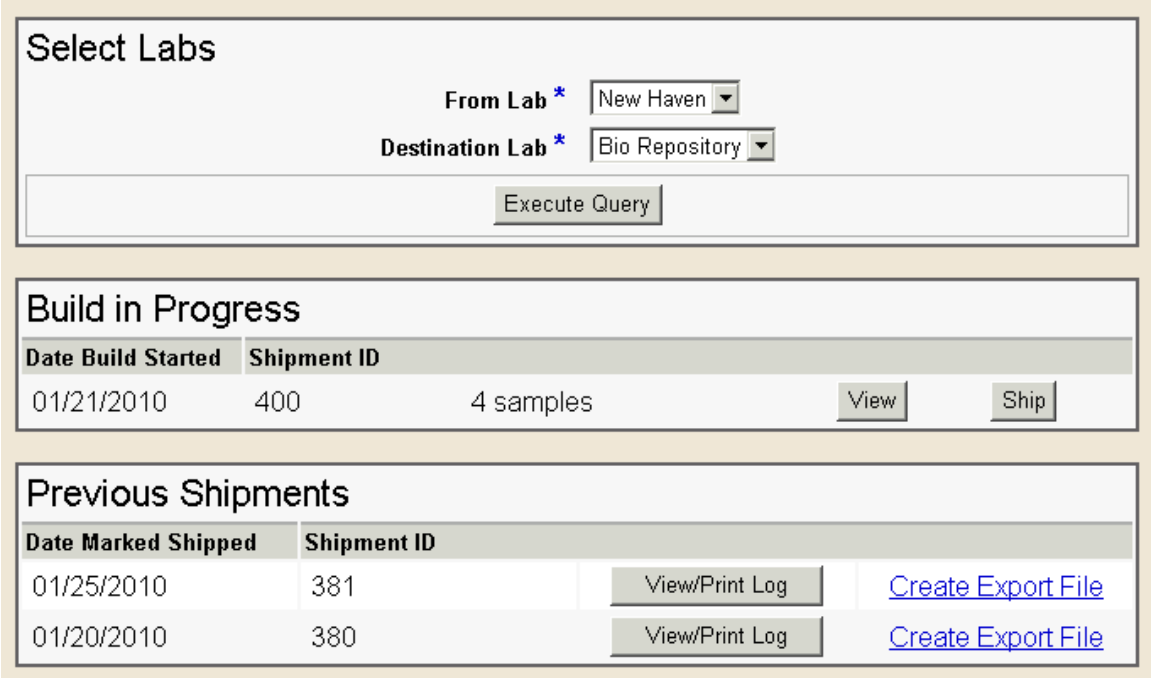


Figure 10-24

- Select a 'From Lab' and a 'Destination Lab' from the drop-down boxes and select the 'Execute Query' button.
- If there is a shipment that has been built for the 'From Lab' and 'Destination Lab' selected and the shipment has not been shipped, the following information will be displayed under the 'Build in Progress' section of the screen: Date Build Started, Shipment ID, number of samples, a 'View' button, and a 'Ship' button.
  - The Date Build Started column will indicate the date the first sample was added to the shipment.
  - The Shipment ID column will indicate the ID assigned to the shipment.
  - The number of samples added to the shipment will be displayed.
  - The 'View' button will allow you to view all of the samples on the shipment as well as details about each sample and a remove link.
  - The 'Ship' button will allow you to view all of the samples on the shipment, a remove link, and mark the samples as shipped.
- Select the 'View' button and the View Shipment screen will be displayed in a new window (see Figure 10-25).

Number of rows returned: 4 Date Build started: 01/21/2010

Barcode	Participant ID	Init	Visit Num	Collection Date	Sample Type	Additive	Container Size	Volume	Remove Samp. from Shipment
AKU7000004	1-1E-5001	JRL	0	01/20/2010	Urine –Tube		2 mL	1.00 mL	Remove
AKU7000005	1-1E-5001	JRL	0	01/20/2010	Urine –Tube		2 mL	1.00 mL	Remove
AKU7000006	1-1E-5001	JRL	0	01/20/2010	Urine –Tube		2 mL	1.00 mL	Remove
AKU7000007	1-1E-5001	JRL	0	01/20/2010	Urine –Tube		2 mL	1.00 mL	Remove

Number of rows returned: 4

Figure 10-25

- The following information will be displayed for each sample in the shipment: Barcode, Participant ID, Initials (Init), Visit Number (Visit Num), Collection Date, Sample Type, Additive, Container Size, Volume, and Remove Sample from Shipment link.
  - The Barcode column will display the barcode for the sample.
  - The Participant ID column will display the ID for the participant for which the sample was collected.
  - The Initials column will display the participant's initials.
  - The Visit Number column will display the visit at which the sample was collected.
  - The Collection Date column will display the date the sample was collected.
  - The Sample Type column will display the type of sample collected.
  - The Additive column will display the additive that was added to the sample.
  - The Container Size column will display the size of the container in which the sample was collected.
  - The Volume column will display the volume of the sample that was collected.
    - The sample volume MUST represent the actual volume in the specific tube.
    - Review the samples as they are scanned into the Shipment and verify that the sample volume listed in the BST matches the sample in the tube.
    - The Remove Sample from Shipment column will display a 'Remove' link to remove the sample from the shipment. Select this link if you want to remove the sample from the shipment.
      - ✓ If a sample volume is incorrect, select the 'Remove' link which will take the sample out of the shipment 'build in progress'.
        - The volume should be corrected through the 'Sample Tracking Update' section of the BST.
        - The sample can then be added into the shipment.
- In addition to the individual sample information, the following shipment information will be displayed: Number of rows returned and Date Build started.
  - The Number of rows returned field will display the number of samples in the shipment.

- The Date Build started field will display the date that the first sample was added to the shipment.

- When you are finished viewing the samples, select the 'Exit View Shipment' link and you will be returned to the Sample Tracking Shipment Area screen.

In order to view a previous shipment:

- Select the 'View Shipments – Mark as Shipped/Print Logs' link on the Biological Sample Tracking Menu.
- The Sample Tracking Shipment Area screen will be displayed on the screen (see Figure 10-26).

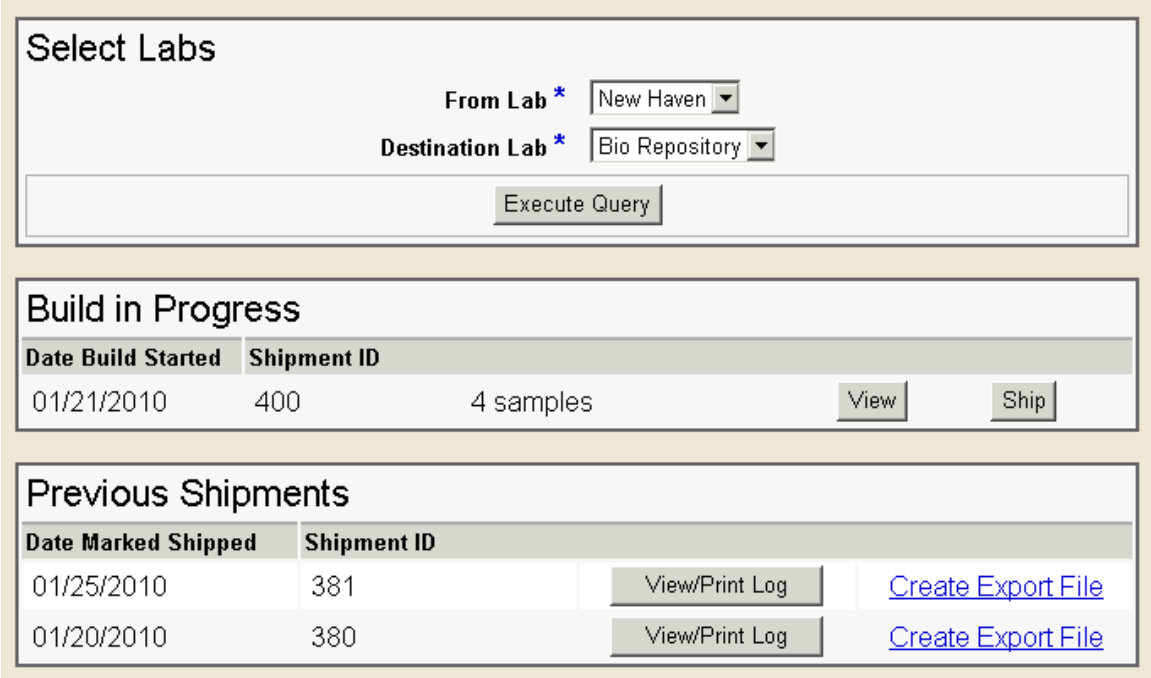


Figure 10-26

- Select a 'From Lab' and a 'Destination Lab' from the drop-down boxes and select the 'Execute Query' button.
- If there are any previous shipments for the 'From Lab' and 'Destination Lab' selected, the following information will be displayed under the 'Previous Shipments' section of the screen: Date Marked Shipped, Shipment ID, a 'View/Print Log' button, and a 'Create Export File' link.
  - The Date Marked Shipped column will indicate the date the shipment was marked shipped.
  - The Shipment ID column will indicate the ID assigned to the shipment.
  - The 'View/Print Log' button will open a new window and display details about the shipment (see Figure 10-27).

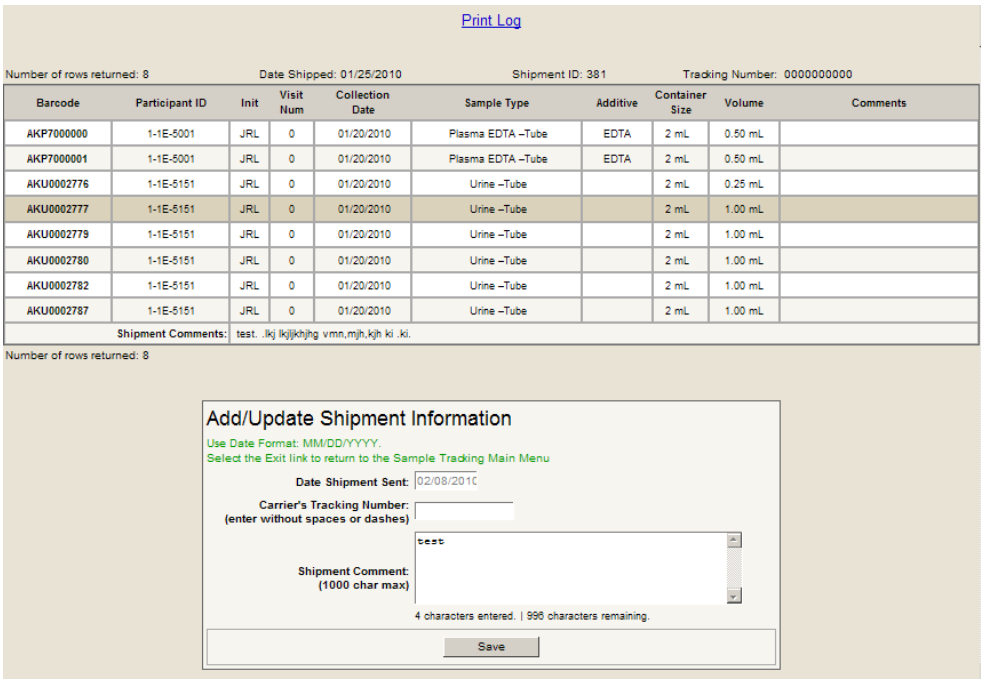


Figure 10-27

- The 'Create Export File' link will open a File Download dialog box asking if you want to open or save the file (see Figure 10-28).

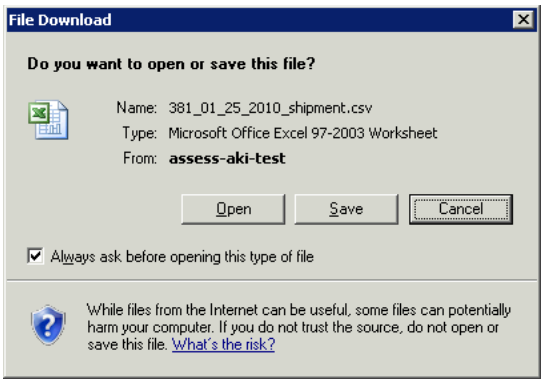
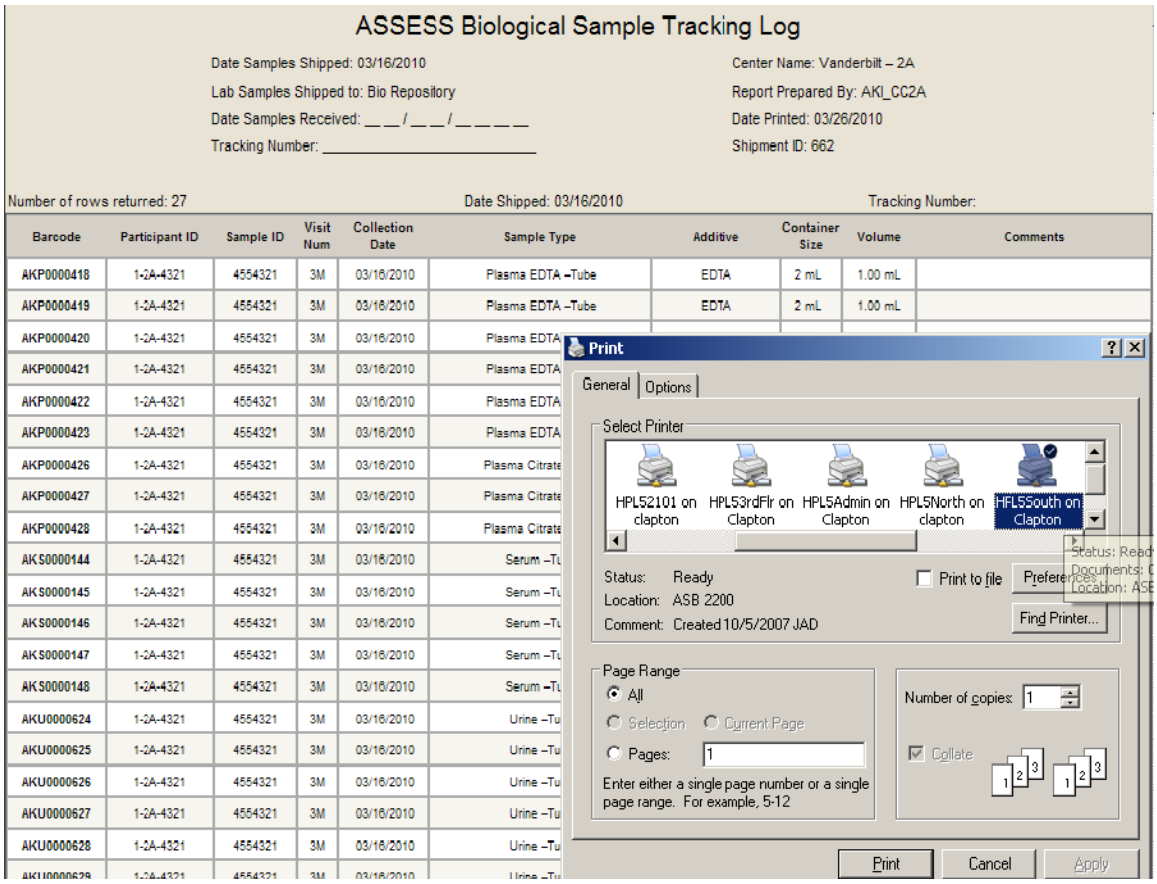


Figure 10-28

- Select the 'View/Print Log' button and the View Shipment screen will be displayed in a new window (see Figure 10-24).
- The following information will be displayed for each sample in the shipment: Barcode, Participant ID, Initials (Init), Visit Number (Visit Num), Collection Date, Sample Type, Additive, Container Size, Volume, and Comments.
  - The Barcode column will display the barcode for the sample.
  - The Participant ID column will display the ID for the participant for which the sample was collected.
  - The Initials column will display the participant's initials.

- The Visit Number column will display the visit at which the sample was collected.
- The Collection Date column will display the date the sample was collected.
- The Sample Type column will display the type of sample collected.
- The Additive column will display the additive that was added to the sample.
- The Container Size column will display the size of the container in which the sample was collected.
  - The Volume column will display the volume of the sample that was collected.
- The Comments column will display comments about the sample.

- In addition to the individual sample information, the following shipment information will be displayed: Number of rows returned, Date Shipped, Shipment ID, Tracking Number, and Shipment Comments.
  - The Number of rows returned field will display the number of samples in the shipment.
  - The Date Shipped field will display the date that the shipment was marked shipped.
  - The Shipment ID field will display the ID assigned to the shipment.
  - The Tracking Number field will display the Carrier's Tracking Number, if the user entered one when marking the samples shipped.
  - The Shipment Comments field will display comments about the shipment, if the user entered any when marking the samples shipped.
- A 'Print Log' link will be displayed at the top of the window. Select this link to open and print an ASSESS Biological Sample Tracking Log for the shipment (see Figure 10-29).



ASSESS Biological Sample Tracking Log

Date Samples Shipped: 03/16/2010
Lab Samples Shipped to: Bio Repository
Date Samples Received: __ __ / __ __ / __ __ __ __
Tracking Number: _____

Center Name: Vanderbilt – 2A
Report Prepared By: AKI_CC2A
Date Printed: 03/26/2010
Shipment ID: 662

Number of rows returned: 27 Date Shipped: 03/16/2010 Tracking Number:

Barcode	Participant ID	Sample ID	Visit Num	Collection Date	Sample Type	Additive	Container Size	Volume	Comments
AKP0000418	1-2A-4321	4554321	3M	03/16/2010	Plasma EDTA –Tube	EDTA	2 mL	1.00 mL	
AKP0000419	1-2A-4321	4554321	3M	03/16/2010	Plasma EDTA –Tube	EDTA	2 mL	1.00 mL	
AKP0000420	1-2A-4321	4554321	3M	03/16/2010	Plasma EDTA				
AKP0000421	1-2A-4321	4554321	3M	03/16/2010	Plasma EDTA				
AKP0000422	1-2A-4321	4554321	3M	03/16/2010	Plasma EDTA				
AKP0000423	1-2A-4321	4554321	3M	03/16/2010	Plasma EDTA				
AKP0000426	1-2A-4321	4554321	3M	03/16/2010	Plasma Citrate				
AKP0000427	1-2A-4321	4554321	3M	03/16/2010	Plasma Citrate				
AKP0000428	1-2A-4321	4554321	3M	03/16/2010	Plasma Citrate				
AKS0000144	1-2A-4321	4554321	3M	03/16/2010	Serum –Tu				
AKS0000145	1-2A-4321	4554321	3M	03/16/2010	Serum –Tu				
AKS0000146	1-2A-4321	4554321	3M	03/16/2010	Serum –Tu				
AKS0000147	1-2A-4321	4554321	3M	03/16/2010	Serum –Tu				
AKS0000148	1-2A-4321	4554321	3M	03/16/2010	Serum –Tu				
AKU0000624	1-2A-4321	4554321	3M	03/16/2010	Urine –Tu				
AKU0000625	1-2A-4321	4554321	3M	03/16/2010	Urine –Tu				
AKU0000626	1-2A-4321	4554321	3M	03/16/2010	Urine –Tu				
AKU0000627	1-2A-4321	4554321	3M	03/16/2010	Urine –Tu				
AKU0000628	1-2A-4321	4554321	3M	03/16/2010	Urine –Tu				

Figure 10-29

- After selecting the link, a print dialog box will open immediately. Select the 'Print' button to print the log or the 'Cancel' button if you do not want to print the log.
- The following information will be displayed on the log for each sample in the shipment: Barcode, Participant ID, Visit Number (Visit Num), Collection Date, Sample Type, Additive, Container Size, Volume, and Comments.
  - The Barcode column will display the barcode for the sample.
  - The Participant ID column will display the ID for the participant for which the sample was collected.
  - The Visit Number column will display the visit at which the sample was collected.
  - The Collection Date column will display the date the sample was collected.
  - The Sample Type column will display the type of sample collected.
  - The Additive column will display the additive that was added to the sample.
  - The Container Size column will display the size of the container in which the sample was collected.
    - The Volume column will display the volume of the sample that was collected.
  - The Comments column will display comments about the sample.

- In addition to the individual sample information, the following shipment information will be displayed: Date Samples Shipped, Lab Samples Shipped to, Date Samples Received, Tracking Number, Center Name, Report Prepared By, Date Printed, Shipment ID, Number of rows returned, and Shipment Comments.
  - The Date Samples Shipped field will display the date that the shipment was marked shipped.
  - The Lab Samples Shipped to field will display the destination to which the samples were shipped.
  - The Date Samples Received field will be a blank date field to be used by the recipient of the shipment.
  - The Tracking Number field will be a blank field to write the carrier's tracking number.
  - The Center Name field will display the origination location of the shipment.
  - The Report Prepared By field will display the User ID of the person who marked the samples as shipped.
  - The Date Printed field will display the current date.
  - The Shipment ID field will display the ID assigned to the shipment.
  - The Number of rows returned field will display the number of samples in the shipment.
  - The Shipment Comments field will display comments about the shipment, if the user entered any when marking the samples shipped.
- When you are finished printing the log, close the ASSESS Biological Sample Tracking Log window and you will be returned to the View Shipment window.
- When you are finished viewing the shipment information, select the 'Exit View Shipment' link and you will be returned to the Sample Tracking Shipment Area.
- Select the 'Create Export File' link to Open or Save a comma-delimited file (i.e., CSV file) of the samples in the shipment to be emailed to the destination lab.
  - After selecting the link, a File Download dialog box will open asking if you want to open or save the file (see Figure 10-28). Select the 'Save' button and a Save As dialog box will open. Select the 'Save' button again to save the file to your desktop.
  - The first three numbers of the filename is the shipment ID followed by the date marked shipped in the following format: MM_DD_YYYY.
- The CSV file contains the following information required by the labs: Barcode, Sample ID, Specimen Type, Volume, UOM, Date Collected, Visit, Additive, Comments, Participant ID and Shipment ID (see Figure 10-30).

	A	B	C	D	E	F	G	H	I	J	K	L
1	Barcode	Sample ID	Specimen	Volume	UOM	Date Colle	Visit	Additive	Comment	Participan	Shipment ID	
2	AKP00011	4521027	P	0.5	mL	6/1/2010	0	E		11C1027	707	
3	AKP00011	4521027	P	0.5	mL	6/1/2010	0	E		11C1027	707	
4	AKP00011	4521027	P	0.5	mL	6/1/2010	0	E		11C1027	707	
5	AKP00011	4521027	P	0.25	mL	6/1/2010	0	E		11C1027	707	
6												

Figure 10-30

- The Barcode column will display the barcode for the sample.
- The Sample ID column will display the RTI code followed by the last four digits of the participant ID for which the sample was collected.
- The Specimen Type column will display a letter identifying the type of specimen. The following codes will be used:
  - D = DNA
  - P = Plasma
  - S = Serum
  - U = Urine
- The Volume column will display the volume of the sample that was collected.
- The UOM column will display the unit of measure for the volume of the sample that was collected.
- The Date Collected column will display the date the sample was collected.
- The Visit column will display the visit at which the sample was collected.
- The Additive column will display a code for the additive that was added to the sample. The following codes will be used:
  - C = Citrate
  - E = EDTA
  - I = Protease Inhibitor
- The Comments column will display comments about the sample.
- The Participant ID column will display the participant ID for which the sample was collected.

- When you are finished viewing the previous shipment, click on the 'Exit Sample Tracking Shipment Area' link, and you will be returned to the Biological Sample Tracking Menu.

In order to mark samples as shipped:

- Select the 'View Shipments - Mark Samples as Shipped/Print Logs' link on the Biological Sample Tracking Menu.
- The Sample Tracking Shipment Area screen will be displayed on the next page (see Figure 10-31).

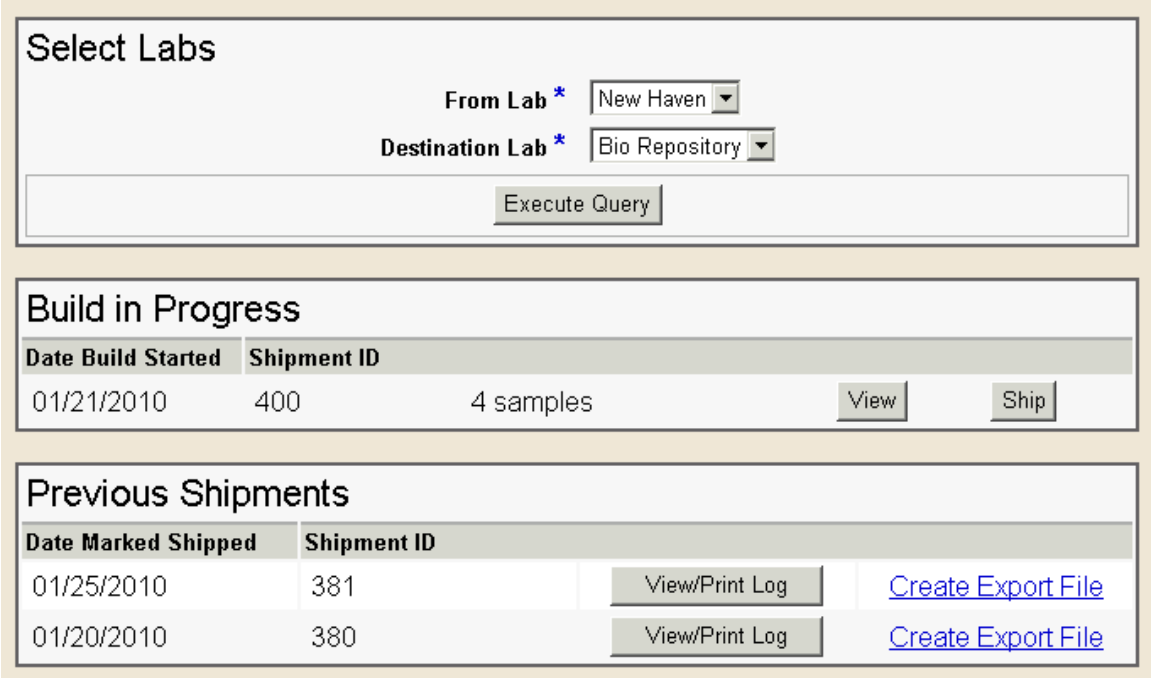


Figure 10-31

- Select a 'From Lab' and a 'Destination Lab' from the drop-down boxes and select the 'Execute Query' button.
- If there is a shipment for the 'From Lab' and' Destination Lab' waiting to be marked as shipped, the following information will be displayed under the 'Build in Progress' section of the screen: Date Build Started, Shipment ID, number of samples, a 'View' button, and a 'Ship' button.
  - The Date Build Started column will indicate the date the first sample was added to the shipment.
  - The Shipment ID column will indicate the ID assigned to the shipment.
  - The number of samples added to the shipment will be displayed.
  - The 'View' button will allow you to view all of the samples in the shipment as well as details about each sample and a 'Remove' link.
  - The 'Ship' button will allow you to view all of the samples in the shipment and mark the samples as shipped.
- Select the 'Ship' button and the Mark as Shipped screen will be displayed in a new window (see Figure 10-32).

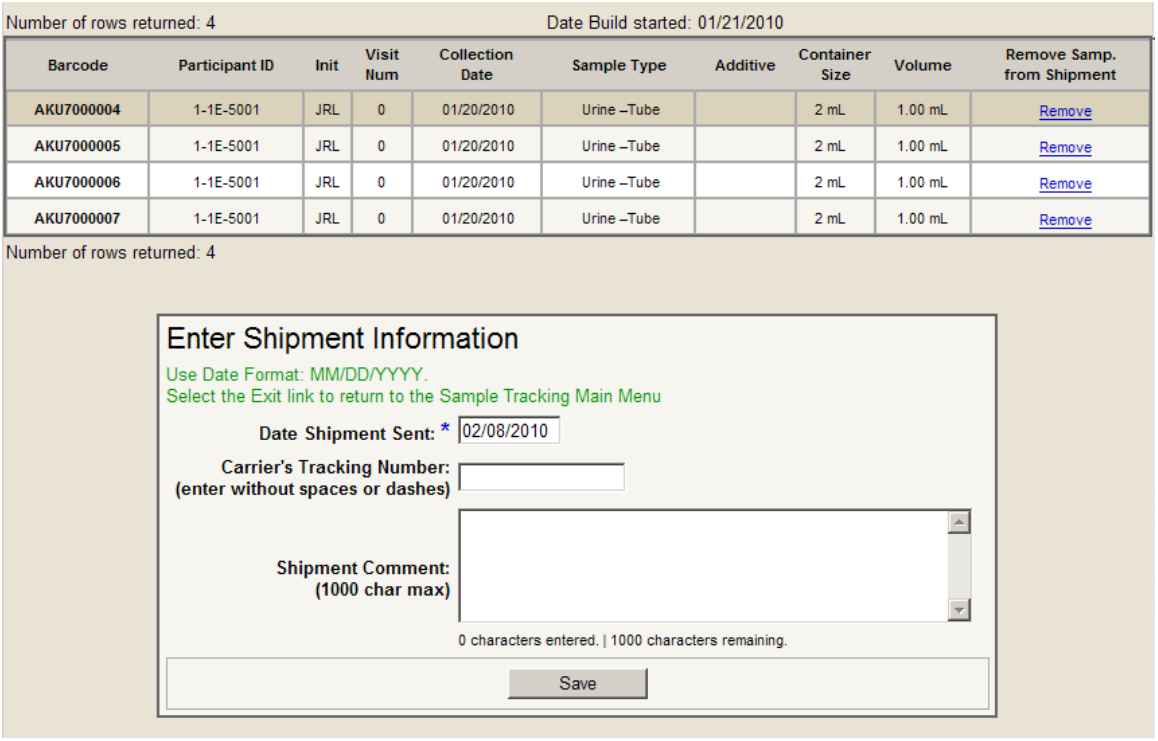


Figure 10-32

- The following information will be displayed for each sample in the shipment: Barcode, Participant ID, Initials (Init), Visit Number (Visit Num), Collection Date, Sample Type, Additive, Container Size, Volume, and Remove Sample from Shipment link.
  - The Barcode column will display the barcode for the sample.
  - The Participant ID column will display the ID for the participant for which the sample was collected.
  - The Initials column will display the participant's initials.
  - The Visit Number column will display the visit at which the sample was collected.
  - The Collection Date column will display the date the sample was collected.
  - The Sample Type column will display the type of sample collected.
  - The Additive column will display the additive that was added to the sample.
  - The Container Size column will display the size of the container in which the sample was collected.
  - The Volume column will display the volume of the sample that was collected.
    - The sample volume MUST represent the actual volume in the specific tube.
    - Review the samples as they are scanned into the Shipment and verify that the sample volume listed in the BST matches the sample in the tube.

- The Remove Sample from Shipment column will display a 'Remove' link to remove the sample from the shipment. Select this link if you want to remove the sample from the shipment.
  - If a sample volume is incorrect, select the 'Remove' link which will take the sample out of the shipment 'build in progress'.
    - ✓ The volume should be corrected through the 'Sample Tracking Update' section of the BST.
    - ✓ The sample can then be added into the shipment.

- In addition to the individual sample information, the following shipment information will be displayed: Number of rows returned and Date Build started.
  - The Number of rows returned field will display the number of samples in the shipment.
  - The Date Build started field will display the date that the first sample as added to the shipment.
- In the 'Enter Shipment Information' section of the screen, the following fields will be displayed: Date Shipment Sent, Carrier's Tracking Number, and Shipment Comment.
  - The Date Shipment Sent field is required and will automatically populate with the current date. If necessary, change this value to the correct date the sample was shipped.
    - A valid shipment date is any date after the collection date and no later than seven days after the current date.
  - The Carrier's Tracking Number field provides a place to enter the tracking number for the shipment. This field is optional.
  - The Shipment Comment field provides a place to enter comments regarding the shipment. The comments will be printed on the shipping log to be included in the box. This field is optional.
- Select the 'Save' button to continue marking the sample(s) as shipped.
- You will be prompted with a message that says, 'Are you sure the data are correct?' If yes and you would like to continue saving, press the 'OK' button. If you would like to make changes to what you have entered, press the 'Cancel' button.
- Once the samples have been marked as shipped, you will receive a confirmation message at the top of the screen in green text 'Date Shipped Successfully Saved' and the following two links: Print Log and Create Export File (see Figure 10-33).
- Select the 'Print Log' link to open and print an ASSESS Biological Sample Tracking Log to send with the samples (See Figure 10-28).
- After selecting the link, a print dialog box will open immediately. Select the 'Print' button to print the log or the 'Cancel' button if you do not want to print the log.
- The following information will be displayed on the log for each sample in the shipment: Barcode, Participant ID, Initials (Init), Visit Number (Visit Num), Collection Date, Sample Type, Additive, Container Size, Volume, and Comments.
  - The Barcode column will display the barcode for the sample.

- The Participant ID column will display the ID for the participant for which the sample was collected.
- The Initials column will display the participant's initials.
- The Visit Number column will display the visit at which the sample was collected.
- The Collection Date column will display the date the sample was collected.
- The Sample Type column will display the type of sample collected.
- The Additive column will display the additive that was added to the sample.
- The Container Size column will display the size of the container in which the sample was collected.
- The Volume column will display the volume of the sample that was collected.
- The Comments column will display comments about the sample.

- In addition to the individual sample information, the following shipment information will be displayed: Date Samples Shipped, Lab Samples Shipped to, Date Samples Received, Tracking Number, Center Name, Report Prepared By, Date Printed, Shipment ID, Number of rows returned, and Shipment Comments.
  - The Date Samples Shipped field will display the date that the shipment was marked shipped.
  - The Lab Samples Shipped to field will display the destination to which the samples were shipped.
  - The Date Samples Received field will be a blank date field to be used by the recipient of the shipment.
  - The Tracking Number field will be a blank field to write the carrier's tracking number.
  - The Center Name field will display the origination location of the shipment.
  - The Report Prepared By field will display the User ID of the person who marked the samples as shipped.
  - The Date Printed field will display the current date.
  - The Shipment ID field will display the ID assigned to the shipment.
  - The Number of rows returned field will display the number of samples in the shipment.
  - The Shipment Comments field will display comments about the shipment, if the user entered any when marking the samples shipped.
- When you are finished printing the log, close the ASSESS Biological Sample Tracking Log window and you will be returned to the Mark as Shipped window.
- Select the 'Create Export File' link to Open or Save a comma-delimited file (i.e., CSV file) of the samples in the shipment to be emailed to the Destination Lab.
  - After selecting the link, a File Download dialog box will open asking if you want to open or save the file (see Figure 10-34). Select the 'Save' button and a Save As dialog box will open. Select the 'Save' button again to save the file to your desktop.

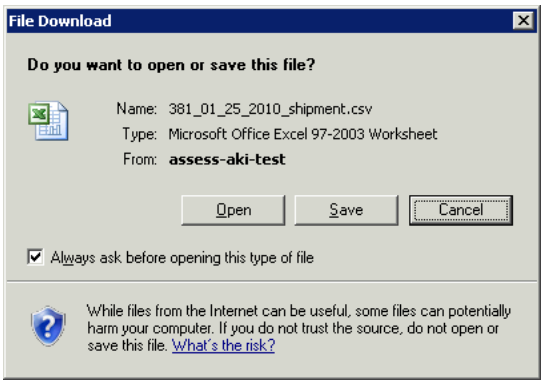


Figure 10-34

- The first three numbers of the filename is the shipment ID followed by the date marked shipped in the following format: MM_DD_YYYY.

- The CSV file contains the following information required by the labs: Barcode, Sample ID, Specimen Type, Volume, UOM, Date Collected, Visit, Additive, Comments, Participant ID and Shipment ID (see Figure 10-35).

	A	B	C	D	E	F	G	H	I	J	K
1	Barcode	Sample ID	Specimen	Volume	UOM	Date Collected	Visit	Additive	Comment	Participan	Shipment ID
2	AKP00004	4554321	P	1	mL	3/16/2010	3M	E		12A4321	662
3	AKP00004	4554321	P	1	mL	3/16/2010	3M	E		12A4321	662
4	AKP00004	4554321	P	1	mL	3/16/2010	3M	E		12A4321	662
5	AKP00004	4554321	P	1	mL	3/16/2010	3M	E		12A4321	662
6	AKP00004	4554321	P	1	mL	3/16/2010	3M	E		12A4321	662
7	AKP00004	4554321	P	5	mL	3/16/2010	3M	E		12A4321	662
8	AKP00004	4554321	P	1	mL	3/16/2010	3M	C		12A4321	662
9	AKP00004	4554321	P	1	mL	3/16/2010	3M	C		12A4321	662
10	AKP00004	4554321	P	1	mL	3/16/2010	3M	C		12A4321	662
11	AKS00001	4554321	S	1	mL	3/16/2010	3M			12A4321	662
12	AKS00001	4554321	S	1	mL	3/16/2010	3M			12A4321	662
13	AKS00001	4554321	S	1	mL	3/16/2010	3M			12A4321	662
14	AKS00001	4554321	S	1	mL	3/16/2010	3M			12A4321	662
15	AKS00001	4554321	S	5	mL	3/16/2010	3M			12A4321	662
16	AKU00006	4554321	U	1	mL	3/16/2010	3M			12A4321	662
17	AKU00006	4554321	U	1	mL	3/16/2010	3M			12A4321	662
18	AKU00006	4554321	U	1	mL	3/16/2010	3M			12A4321	662
19	AKU00006	4554321	U	1	mL	3/16/2010	3M			12A4321	662
20	AKU00006	4554321	U	1	mL	3/16/2010	3M			12A4321	662
21	AKU00006	4554321	U	1	mL	3/16/2010	3M			12A4321	662
22	AKU00006	4554321	U	1	mL	3/16/2010	3M			12A4321	662
23	AKU00006	4554321	U	1	mL	3/16/2010	3M			12A4321	662
24	AKU00006	4554321	U	1	mL	3/16/2010	3M			12A4321	662
25	AKU00006	4554321	U	10	mL	3/16/2010	3M			12A4321	662

Figure 10-35

- The Barcode column will display the barcode for the sample.

- The Sample ID column will display the RTI code followed by the last four digits of the participant ID for which the sample was collected.
- The Specimen Type column will display a letter identifying the type of specimen. The following codes will be used:
  - D = DNA
  - P = Plasma
  - S = Serum
  - U = Urine
- The Volume column will display the volume of the sample that was collected.
- The UOM column will display the unit of measure for the volume of the sample that was collected.
- The Date Collected column will display the date the sample was collected.
- The Visit column will display the visit at which the sample was collected.
- The Additive column will display a code for the additive that was added to the sample. The following codes will be used:
  - C = Citrate
  - E = EDTA
  - I = Protease Inhibitor
- The Comments column will display comments about the sample.
- The Participant ID column will display the participant ID for which the sample was collected.

- When you are finished printing the log file and saving the export file, select the 'Exit Mark as 'Shipped' link and you will be returned to the Sample Tracking Shipment Area screen.

In order to search or view biological sample tracking information:

- Select the 'Enter/Update/Search Sample Tracking' link on the Biological Sample Tracking Menu.
- The Enter/Update/Search Sample Tracking screen (see Figure 10-36) will be displayed on the screen.

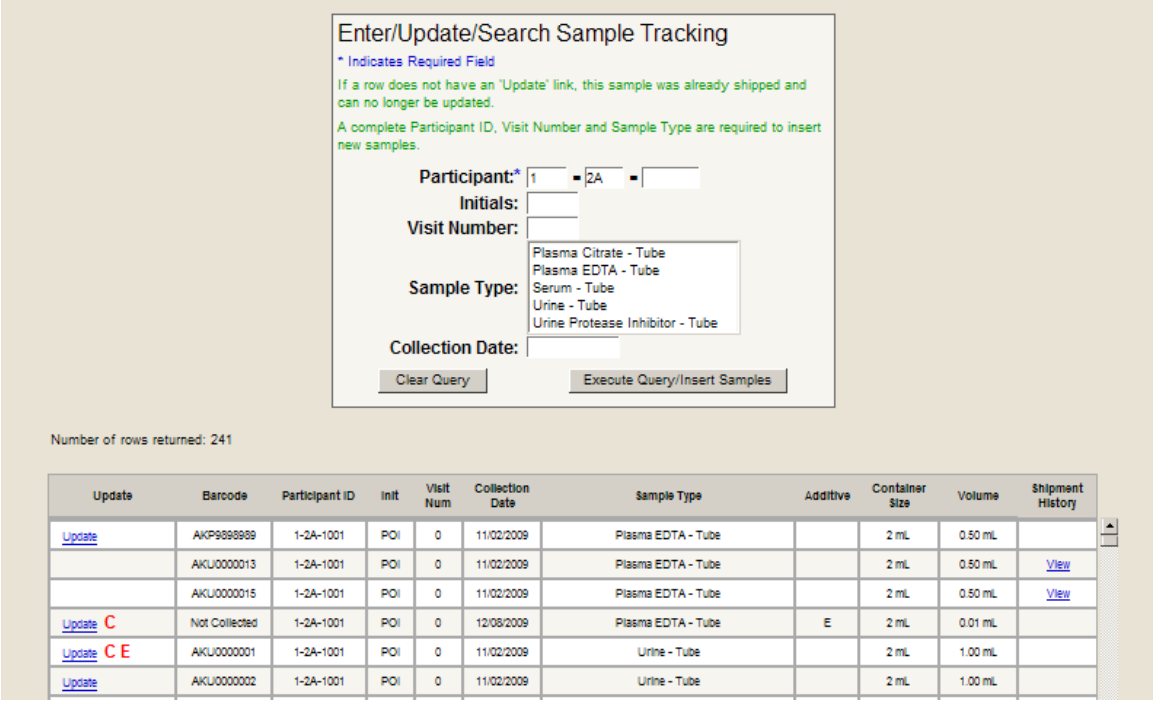


Figure 10-36

- Protocol Number is required and all other fields are optional for the search query.
- If you want to query all biological sample tracking data, enter the protocol number and select the 'Execute Query/Insert Samples' button.
- If you want to narrow your search criteria, you may provide any combination of the values listed below.
  - Participant allows you to limit your search to a specific participant's samples.
    - If you entered the Biological Sample Tracking screens by way of the Direct Module Access heading on the ASSESS-AKI Main Menu screen, you will be required to enter a valid protocol number. If you entered through the protocol Main Menu, the protocol number will be displayed automatically.
  - Visit Number allows you to limit your search to samples collected at a specific visit.
  - Sample Type allows you to limit your search to one of the samples being tracked in the system.
  - Collection Date allows you to limit your search to samples collected on a particular date.
- Select the 'Execute Query/Insert Samples' button to run your search.
- In the results section of the page, you will see information displayed for the following fields (see Figure 10-36): Update, Barcode, Participant ID, Initials (Init.), Visit Number (Visit Num), Collection Date, Sample Type, Additive, Container Size, Volume, and Shipment History.
  - The Update column will display an Update link for samples that may be updated.

- For some samples, there may be a red 'C' or 'E' next to the Update link. The 'C' indicates that a comment has been entered by the center or the lab for this sample while the 'E' indicates that a sample was excluded from the shipment by the center or the lab.
- To view the comment or exclusion, select the red 'C' or 'E' and a new window will open and display all comments as well as the exclusion reason (see Figure 10-37).

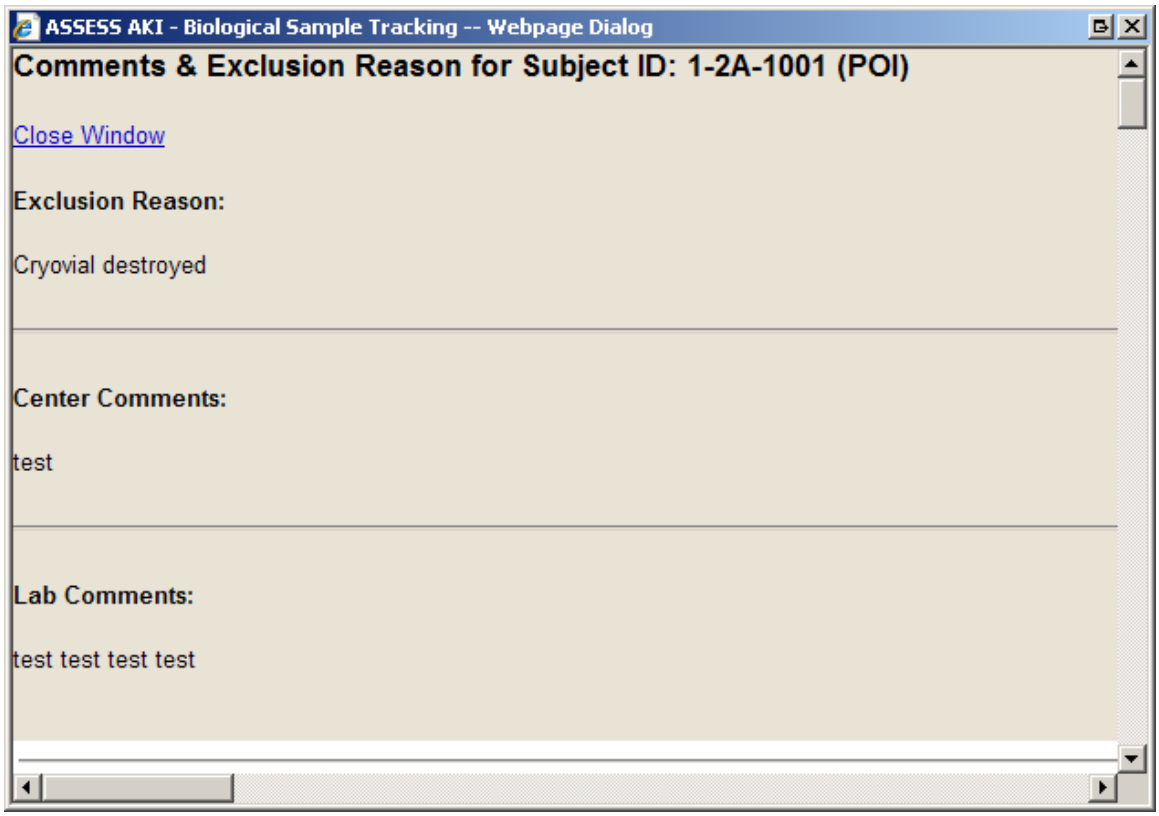


Figure 10-37

- The Barcode column will display the barcode for the sample if it was collected or the text 'Not Collected' if the sample was not collected.
- The Participant ID column will display the ID for the participant for which the sample was collected.
- The Initials column will display the participant's initials.
- The Visit Number column will display the visit at which the sample was collected.
- The Collection Date column will display the date the sample was collected.
- The Sample Type column will display the type of sample collected.
- The Additive column will display a code for the additive that was added to the sample. Additive codes are as follows:
  - C = Citrate

- E = EDTA
- P = Protease Inhibitor

- The Container Size column will display the size of the container in which the sample was collected.
- The Volume column will display the volume of the sample that was collected.
- The Shipment History column will display a 'View' link if there is shipment history to view.
  - To view the shipment history, select the 'View' link and a new window will open and display the Shipment History (see Figure 10-38).

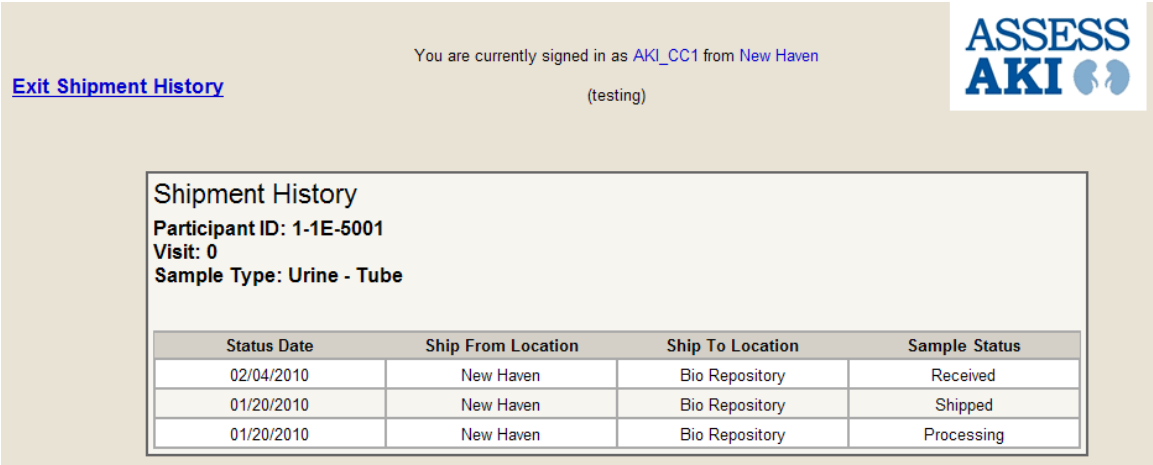


Figure 10-38

- The Shipment History window will display the Participant's ID, Visit and Sample Type as well as the following information for each phase of the shipment process: Status Date, Ship From Location, Ship To Location, and Sample Status.
  - ✓ Status Date column will display the date that the shipment status for the sample changed. The most current status will be listed first.
  - ✓ Ship From Location column will display where the sample originated.
  - ✓ Ship To Location column will display the sample's destination.
  - ✓ Sample Status column will display where the sample is within the shipment process. There are three shipment statuses:
    - 'Received' means the sample has been received by the Ship To Location.
    - 'Shipped' means the sample has been shipped from the Ship From Location.
    - 'Processing' means the sample has been put into a shipment, but it has not been shipped yet.

- When you are finished viewing the Shipment History, select the 'Exit Shipment History' link to return to the Enter/Update/Search Sample Tracking screen.

10.B.6 Data Corrections

The individuals who can access this module are: Data Management staff and Research Coordinators.

In order to query current data corrections:

- Select the 'Data Corrections' link under the Editing heading on the protocol Main Menu.
- The Data Corrections setup screen (see Figure 10-39) will be displayed on the next screen.
- All fields are optional for this query, except the order by option. If you want to query all data corrections, choose the Sort option you want for the results by clicking the appropriate Order By radio button and press the 'Execute Query' button.
- If you want to narrow your search criteria, you can provide any combination of the values listed below.
- Enter a valid participant ID in the Participant ID field.
  - The protocol will auto-populate based on the protocol the user is currently logged into.
  - Note: If the participant has not been enrolled in this protocol, you will receive a pop-up message that says "The participant ID has not been enrolled in this protocol." Once you press the 'OK' button, the participant ID and initials field will be cleared out and the cursor will move back to the participant ID field.
- The Initials field will populate once the entire Participant ID field has been completed.
- Enter a valid visit number in the Visit Number field.
  - Note: If the visit number is not valid for the current protocol, you will receive a pop-up message that says, "This is not a valid visit number for this protocol. Valid visit numbers include: 0, 3M, 6M, 12M, 18M, 24M, 30M, 36M, 42M, 48M, 54M, 60M, 66M, 72M, 78M, 84M, 90M."
- Enter a valid date in the Visit Date field.
  - The date entered must be between the protocol start date and the current date.
- Choose a form by clicking on the 'F' button. In the box provided, choose the form name you would like and press the 'OK' button.
  - You cannot type into the Form Name field on the query screen. That field will auto-populate with the value you choose in the drop-down.
  - If you would like to limit the forms displayed in the drop-down, you can start typing in the empty field above the form names. The application uses pattern matching to limit the form names to ones that look like what you have typed in the field.
  - You cannot choose more than one form from the drop-down.
- Choose a form type by clicking the down arrow and highlighting the type you want.

  - Typical form types include P, S, T, and C. P is used to identify packet forms, S is used to identify single forms, T is used to identify tracking forms, and C is used to identify concurrent forms.

- Choose a data correction type by clicking the down arrow and highlighting the type you want: 1, 2, or 3.
  - Type designates who originated the data correction and in the case of the data managers, what type of correction was made.
  - Type 1 designates that a Research Coordinator added the data correction.
  - Type 2 designates that a Project or Data Specialist added the data correction. Primary and Secondary Data Managers are also allowed to enter Type 2 data corrections when the correction added is of the same type that would typically be entered by the Project and Data Specialists.
  - Type 3 designates that a Primary Data Manager added the data correction.
- Choose the data correction status by clicking the down arrow and highlighting the status you want: Hold, DCC, Center, or Closed.
  - The Hold status is used when someone from the DCC is looking into something or is waiting on information sent from the coordinators and cannot proceed with the data correction until that information is received.
  - The DCC status is used when a Data Manager is working on the data correction. Research Coordinators can "send" a data correction to the Data Manager, by changing the status to DCC.
  - The Center status is used when a Research Coordinator is working on the data correction.
  - The Closed status is used when the Research Coordinator or Data Manager feels that a correction has been resolved.
- Choose how the results will be displayed by choosing one of the Order By radio buttons.
  - The Participant ID order will display records in the order of Protocol Number, Center Number, and Participant Number. The records will be ordered by Visit Number, Form Name, Form Type, Visit Date, and Data Correction Type.
  - The Oldest order will display the records based on the most recent Data Correction Status change that is reflected in the Days column. The records will be displayed with the highest number of days to the least number of days. The records will be ordered by Protocol Number, Center Number, Participant Number, Visit Number, Form Name, Form Type, Visit Date, and Data Correction Type.
  - The Status order will display records by the Data Correction Status in alphabetical order. The records will be ordered by Protocol Number, Center Number, Participant Number, Visit Number, Form Name, Form Type, Visit Date, and Data Correction Type.
- Press the 'Execute Query' button.
- In the results section of the page, you will see information displayed for the following fields (see Figure 10-40): Edit link, Delete link, Participant ID, Status, Days, Visit Number (Vnum), Visit Date

(V_Date), Form Name, Form Type, Data Correction Type (DC Type), Primary Field (Prim Field), Record ID (Rec ID), Original Value (Orig Val), Corrected Value (Corr Val), and Last Comment.

- The Edit link will appear for all data correction records.
- The Delete link will appear for all data correction records that can be deleted.
  - See the section below describing how to delete a record for additional information on which rows can be deleted.
- The Days column will show how many days it has been since the status has been changed. All closed data corrections will be set to 0 days.
- The Primary Field column will display the field that the correction is related.
- The Record ID column is typically used for repeating forms and will display the specific record that was modified.
- The Original Value column will display the value that was entered prior to making the correction.
- The Corrected Value column will display the value to which the original value was changed. .
- The Last Comment column will display the most recent comment added for this data correction.

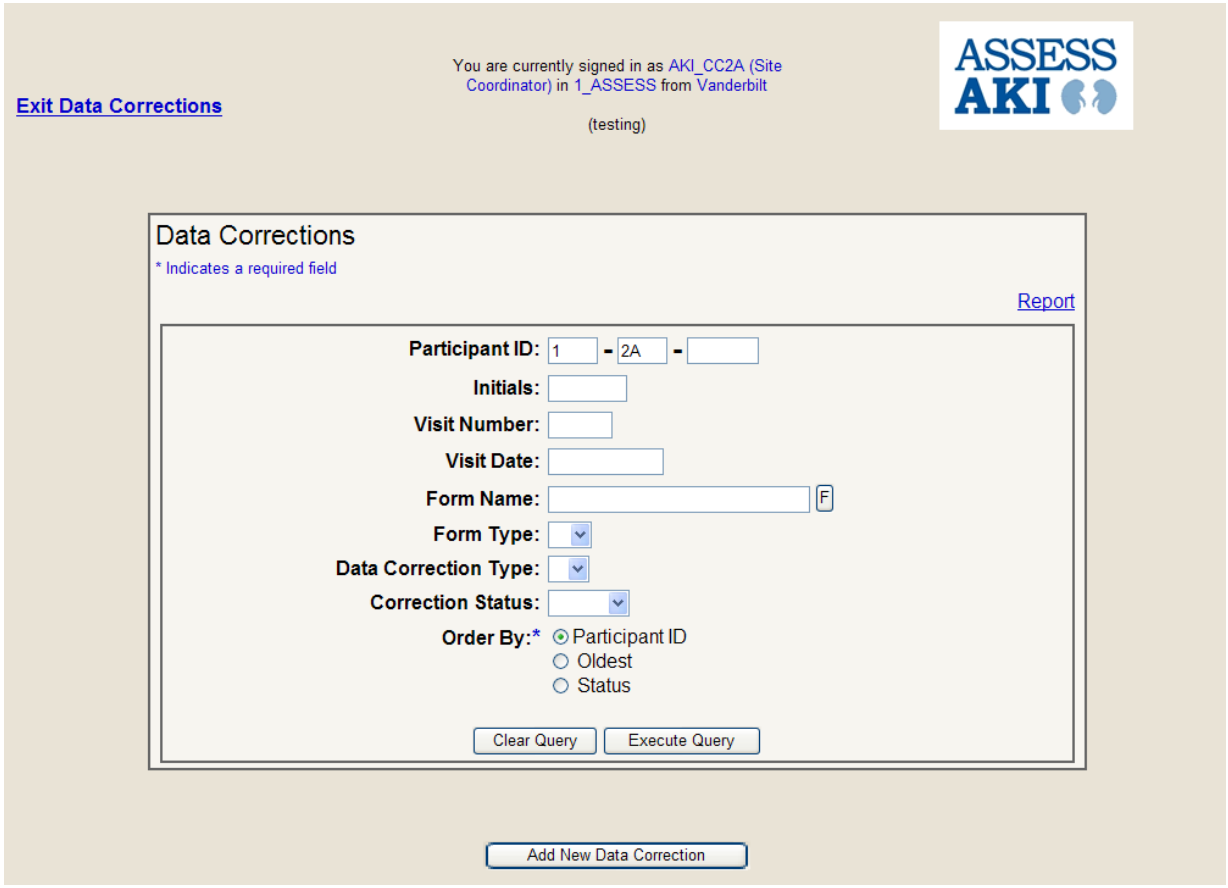


Figure 10-39

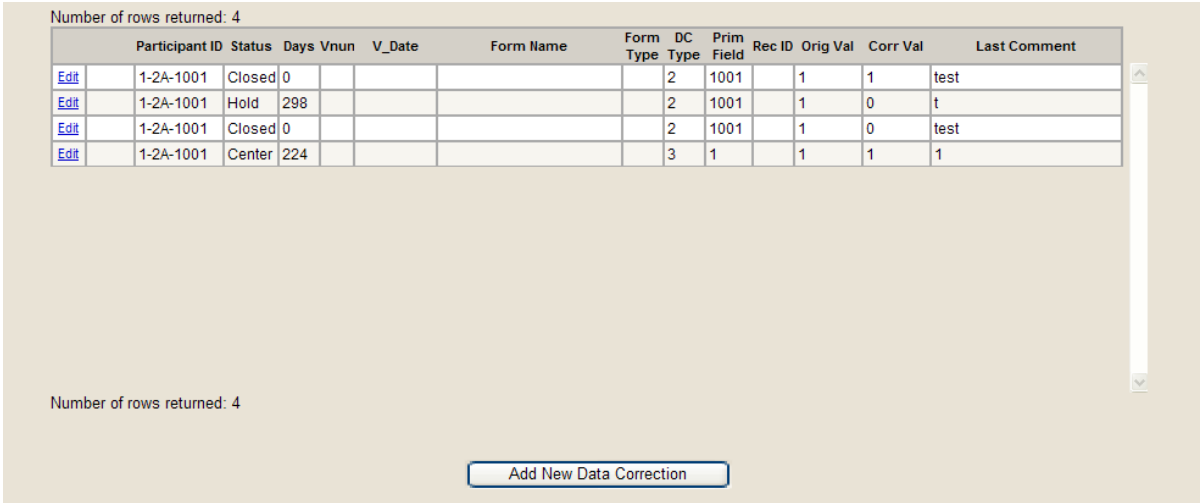


Figure 10-40

In order to add a new data correction:

- Press the 'Add New Data Correction' button at the bottom of the screen.
  - This will open another window in which the data correction information can be entered (see Figure 10-40).
- The following fields are required: Participant ID, DC Type, Prim Field, Orig Value, Correct Value, Status, and Comment.
- Enter a valid participant ID in the Participant ID field.
  - The protocol will auto-populate based on the protocol the user is currently logged into.
  - Note: If the participant has not been enrolled in this protocol, you will receive a pop-up message that says "The participant ID has not been enrolled in this protocol." Once you press the 'OK' button, the participant ID and initials field will be cleared out and the cursor will move back to the participant ID field.
- The Initials field will populate once the entire Participant ID field has been completed.
- Enter a valid visit number in the Visit Number field.
  - Note: If the visit number is not valid for the current protocol, you will receive a pop-up message that says, "This is not a valid visit number for this protocol. Valid visit numbers include: 0, 3M, 6M, 12M, 18M, 24M, 30M, 36M, 42M, 48M, 54M, 60M, 66M, 72M, 78M, 84M, 90M ."
- Enter a valid date in the Visit Date field.
  - The date entered must be between the protocol start date and the current date.
- Choose a form by clicking on the 'F' button. In the box provided, choose the form name you would like and press the 'OK' button.
  - You cannot type into the Form Name field on the query screen. That field will auto-populate with the value you choose in the drop-down.
  - If you would like to limit the forms displayed in the drop-down, you can start typing in the empty field above the form names. The application uses pattern matching to limit the form names to ones that look like what you have typed in the field.
  - You cannot choose more than one form from the drop-down.
- Choose a form type by clicking the down arrow and highlighting the type you want.
  - Typical form types include P, S, T, and C. P is used to identify packet forms, S is used to identify single forms, T is used to identify tracking forms, and C is used to identify concurrent forms.
- The data correction type will auto-populate based on the user logged on.
  - The DC type designates who originated the data correction.
  - Type 1 designates that a Research Coordinator added the data correction.

  - Type 2 designates that a Project or Data Specialist added the data correction. Data Managers are also allowed to enter Type 2 data corrections when the correction added is of the same type that would typically be entered by the Project and Data Specialists.
  - Type 3 designates that a Primary Data Manager added the data correction.
- Enter the record referenced in the data correction for repeating forms in the Record ID field.
- Enter the field on the form that is being changed in the Prim Field field.
- Enter the value that was entered in the Prim Field before it was changed in the Orig Value field.
- Enter the new value that will replace the Orig Value in the Correct Value field.
  - If the Correct Value is longer than the space provided, enter "See Comment" in the Correct Value text box and use the Comment text area to provide the correct value.
- Choose the data correction status by clicking the down arrow and highlighting the status you want: Hold, DCC, Center, or Closed.
  - The Hold status is used when someone from the DCC is looking into something or is waiting on information sent from the coordinators and cannot proceed with the data correction until that information is received.
  - The DCC status is used when a Primary Data Manager is working on the data correction. Research Coordinators can "send" a data correction to the Primary Data Manager, by changing the status to DCC.
  - The Center status is used when a Research Coordinator is working on the data correction.
  - The Closed status is used when the Research Coordinator or Primary Data Manager feels that a correction has been resolved.
- Enter additional information about this data correction in the Comment field.
  - All users are required to enter a comment when adding a new data correction.
- Press the 'Save' button.
  - If the record was saved to the database successfully, you will get a prompt that says, "Your new Data Correction has been successfully saved. Would you like to add another Data Correction?" If you have more data corrections to add, press the 'OK' button and you will be taken back to a blank Add a Data Correction window. Otherwise, press the 'Cancel' button and you will be taken back to the initial Data Corrections screen.
- If you have made a mistake and would like to start over, press the 'Cancel' button on the Add a Data Correction window and you'll be taken to the initial Data Corrections screen.

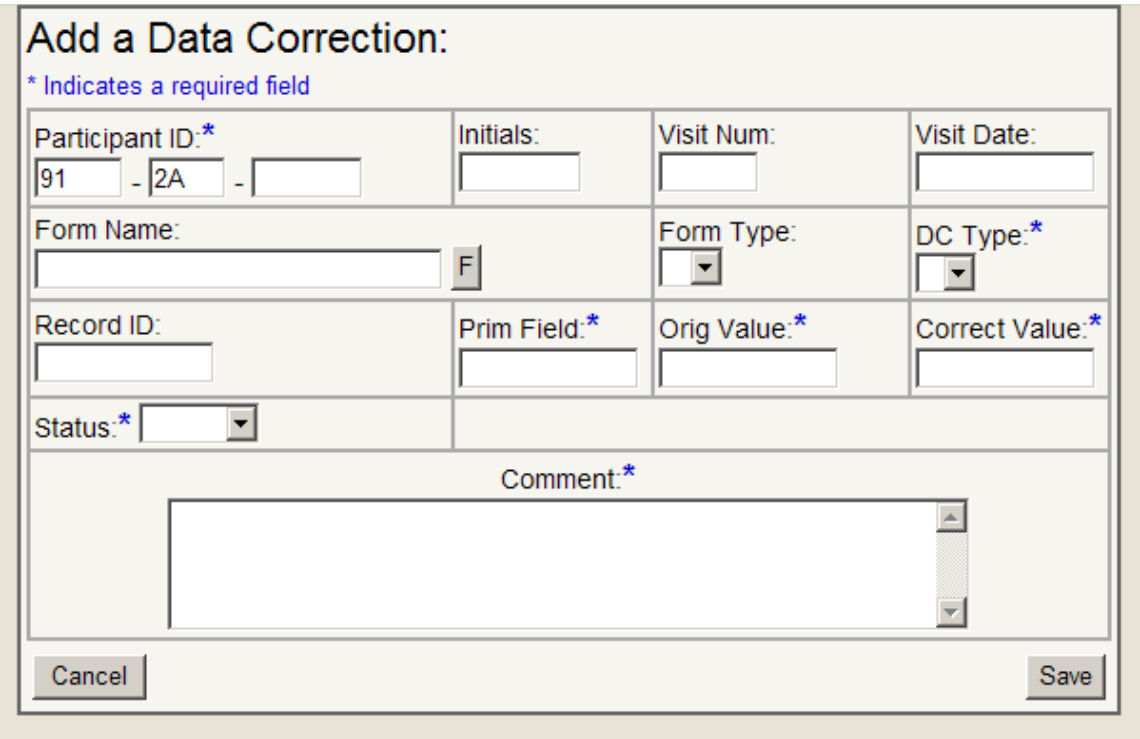


Figure 10-40

In order to add a comment to an existing data correction:

- Perform the above steps to query up the data correction that you want to modify.
- Press the 'Edit' link next to the correction you want to modify.
- Type a comment into the Add a New Comment field.
- Press the 'Save' button.
  - If the record was saved to the database successfully, you will get a prompt that says, "The Data Correction was successfully updated."

In order to change the status of an existing data correction:

- Perform the above steps to query up the data correction that you want to modify.
- Press the 'Edit' link next to the correction you want to modify.
- Change the status by clicking on the down arrow of the Status drop-down menu and choosing the desired value.
  - Research Coordinator can change the status in the following manner:
    - Center -> Closed
    - Center -> DCC
    - Closed -> DCC

- Project and Data Specialists can change the status in the following manner:
  - Closed -> Center
  - Hold -> Center
- Primary Data Managers and Senior Data Management Analysts can change the status in the following manner:
  - Closed -> Center
  - Closed -> Hold
  - DCC -> Center
  - DCC -> Closed
  - DCC -> Hold
  - Hold -> Center
  - Hold -> Closed

- Enter a comment in the Add a New Comment field.
- Press the 'Save' button.
  - If the record was saved to the database successfully, you will get a prompt that says, "The Data Correction was successfully updated."

In order to delete a current data correction:

Perform the above steps to query up the data correction that you want to modify.

The following limitations apply to deleting data corrections:

- If the user is a Research Coordinator, he/she can only delete rows if the Data Correction Type is 1, the Correction Status is Center or DCC and the user performing the delete is the same user who entered the comment.
- If the user is a Project and Data Specialist, he/she can only delete rows if the Data Correction Type is 2, the Correction Status is Hold or Center, there is at most 1 comment, and the user performing the delete is the same user who entered the comment.
- If the user is a Primary Data Manager or a Senior Data Management Analyst, any data correction can be deleted.

- Click the 'Delete' link next to the row to be deleted.
- You will be prompted with a message that says, "Are you sure you want to delete this Data Correction?"
  - If you still would like to proceed, press the 'OK' button.
  - If the record was deleted from the database successfully, you will get a green message at the top of the Data Corrections screen that says, "Data Correction deleted successfully."
  - If not, press the 'Cancel' button and you will be taken back to the Data Corrections screen.

10.B.7 Editor

The individuals who can access this module are: Data Management staff and Research Coordinators.

This module allows DCC and Center personnel to view and edit information previously entered into electronic packet, single or concurrent forms. After saving any changes, the error checks are re-executed and errors will be displayed on a report.

The setup screen will allow you to enter a variety of criteria. The criteria are: Participant ID (including protocol number, center number and participant number), Visit Number, and Form Type.

- All of the search criteria options on this screen, with the exception of the Form Type, are optional.
  - If the 'Single with Date' Form Type radio button is selected, the date is required.
- Enter a valid participant ID in the Participant ID field.
  - The protocol will auto-populate based on the protocol the user is currently logged into.
  - The center number will auto-populate for center users based on the user who is currently logged on.
  - Note: If the participant has not been enrolled in this protocol, you will receive a pop-up message that says "The participant ID has not been enrolled in this protocol." Once you press the 'OK' button, the Participant ID and Initials field will be cleared out and the cursor will move back to the participant ID field.
- The Initials field will populate once the entire Participant ID field has been completed.
- Enter a valid visit number in the Visit Number field.
  - Note: If the visit number is not valid for the current protocol, you will receive a pop-up message that says, "This is not a valid visit number for this protocol. Valid visit numbers include: 0, 3M, 6M, 12M, 18M, 24M, 30M, 36M, 42M, 48M, 54M, 60M, 66M, 72M, 78M, 84M, 90M."
- Choose which types of forms you would like returned in the search by selecting the appropriate radio button: Packet & Single, Packet, Single, Single with Date, or Concurrent.
  - If choosing the Single with Date radio button, a valid date must be supplied in the adjacent field.
    - A valid date is any date between the protocol start date and the current date.
  - When selecting the 'Packet & Single' radio button, the search will return all packet and single forms in that protocol that have been entered at the site, but have not been logged as received at the DCC.
  - When selecting the 'Packet' radio button, the search will return all packet forms in that protocol that have been entered at the site, but have not been logged as received at the DCC.
  - When selecting the 'Single' radio button, the search will return all the single forms in that protocol that have been entered at the site, but have not been logged as received at the DCC.
  - When selecting the 'Single with Date' radio button, the search will return all single forms in that protocol that have been entered at the site and whose visit date falls on the date entered in the

field adjacent to the 'Single with Date' radio button, but have not been logged as received at the DCC.

- When selecting the 'Concurrent' radio button, the search will return all concurrent forms in that protocol that have been entered at the site, but have not been logged as received at the DCC.
  - The Visit Number field will be disabled and should not allow any values to be typed in by the user.

In order to modify a form:

- Select the 'Editor' link under the Editing heading on the protocol Main Menu.
- Enter the desired criteria in the setup screen as described above.
- Press the 'Execute Query' button.
- The results of your search will be displayed below the search area (see Figure 10-41). The information displayed is: Participant ID, Visit, Form Name, Type, Visit Date, and Date Entered.
- Once you have located the form you want to edit, click anywhere on that row.
- The form that you chose will appear in a new window. The form will be pre-filled with the previously entered data.
- You can then make the desired changes to the data with the following limitations:
  - Research Coordinators are only permitted to view and edit form information that was entered by a Research Coordinator user and is not logged as received at the DCC.
  - Forms cannot be marked missing.
  - For single forms, the visit date can be modified as long as the new visit date is different from all other single forms with the same name entered at the same visit.
  - The following constraints apply to repeating forms only:
    - Forms cannot be marked missing.
    - Once you click in the table to make modifications to the data, you can no longer add or delete a record. You must first press the 'Save' button and you will then be permitted to add or delete a record.
    - The record ID field cannot be modified. This is typically a value that uniquely identifies each row on a repeating form.
    - Deleted records will not be recovered when pressing the 'Exit' button. As soon as you click the 'Delete' link and press the 'OK' button on the message that follows, the row has been deleted. If you change your mind about deleting a record, you must press the 'Cancel' button on the "Are you sure you want to delete this record?" message.
    - Added records will not be removed when pressing the 'Exit' button. As soon as you click the 'Add' link and press the 'Save' button at the bottom of the screen, the row has been added. If you change your mind about adding a record, you must either press the 'Cancel' button above the record during entry or after the record has been saved by clicking the 'Delete' link above that record.

- Once all the desired changes have been made, press the 'Save' button.
  - The form will be revalidated at this point and any errors that exist will be saved into the database.
  - Errors should be handled the same as they are during Entry.
- If you would like to cancel any modifications you have made or to return to the Editor screen, press the 'Exit' button.
  - Any errors that exist for the form will be displayed on the Entry Errors Report that will load in another Internet browser window.
    - The following fields will be displayed on the report: Participant, Visit, Form, Form Type, Visit Date, Record ID (if applicable), Error, Field, Original Value, Correct Value, and Error Message.

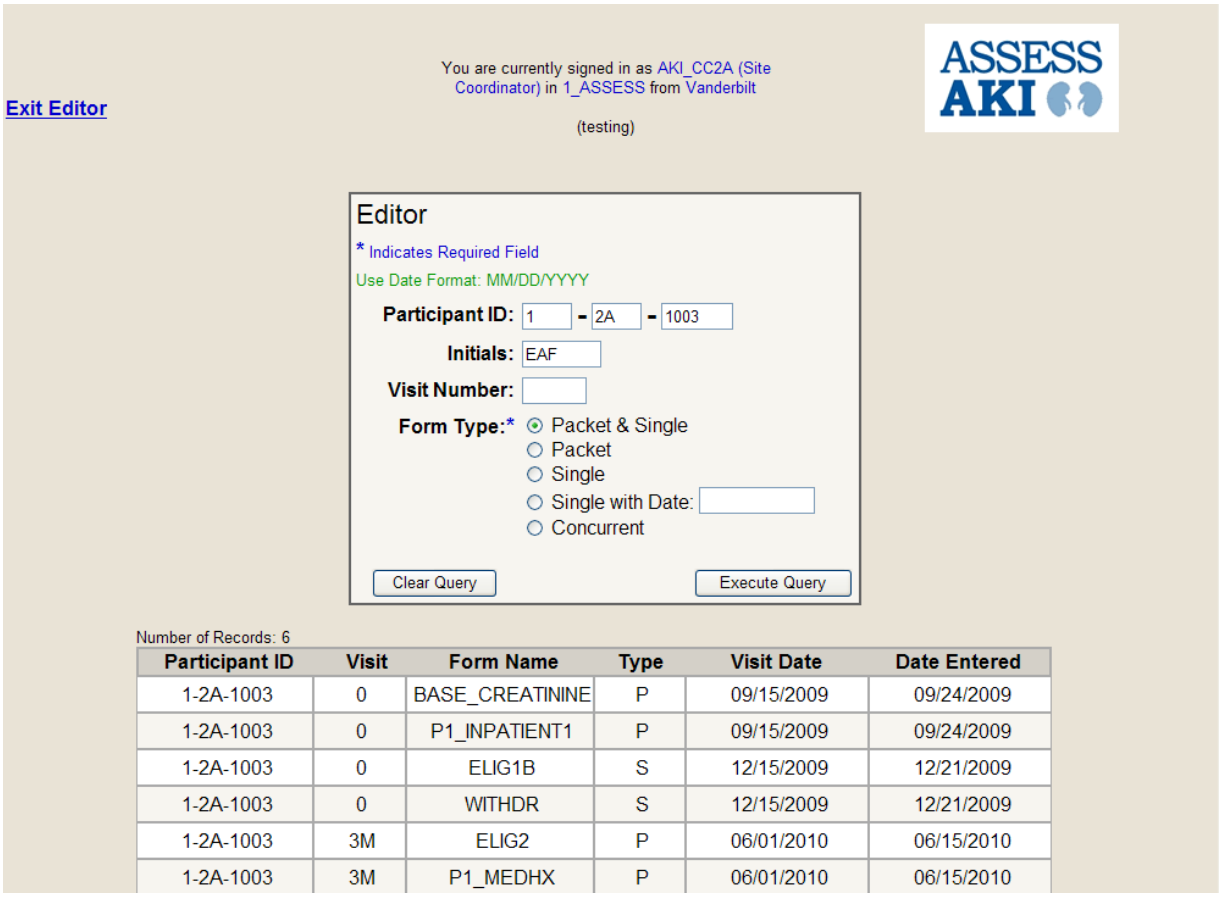


Figure 10-41

10.B.8 Error Tracking

The individuals who can access this module are: Data Management staff and Research Coordinators.

This module provides the DCC and Center staff with the ability to view, track, and resolve data errors.

- The Center staff is able to view entry errors until the forms are received at the DCC, mark multiple and single errors as unresolvable, and provide responses to queries sent by the DCC.
- After clicking the 'Execute Search' button, do not click on any links on the page until the page has refreshed completely.

In order to query existing errors:

- Select the 'Error Tracking' link under the Editing heading on the protocol Main Menu.
- The Error Tracking setup screen will be displayed on the next page (see Figure 10-42).
- No fields are required to be entered on this screen.
- Enter a valid participant ID in the Participant ID field.
  - The protocol will auto-populate based on the protocol the user is currently logged into.
  - The center number will auto-populate for center users based on the user who is currently logged on.
  - Note: If the participant has not been enrolled in this protocol, you will receive a pop-up message that says "The participant ID has not been enrolled in this protocol." Once you press the 'OK' button, the Participant ID and Initials field will be cleared out and the cursor will move back to the participant ID field.
- The Initials field will populate once the entire Participant ID field has been completed.
- Enter a valid visit number in the Visit Number field.
  - Note: If the visit number is not valid for the current protocol, you will receive a pop-up message that says, "This is not a valid visit number for this protocol. Valid visit numbers include: 0, 3M, 6M, 12M, 18M, 24M, 30M, 36M, 42M, 48M, 54M, 60M, 66M, 72M, 78M, 84M, 90M."
- Select a form name in the Form Name field by clicking on the 'F' button.
  - This will open another screen that will allow you to choose which form name you would like from a list.
  - Multiple form names can be selected by using the Ctrl or Shift keys on the keyboard.
  - If you would like to limit the forms displayed in the drop-down, you can start typing in the empty field above the form names. The application uses pattern matching to limit the form names to ones that look like what you have typed in the field.
  - Highlight the form(s) you would like and press the 'OK' button. You will be returned to the Error Tracking setup screen.
- Select the form type you would like to search on by clicking the Form Type drop-down and choosing the desired value from the list.

- Select an error check type in the Error Check Type field by clicking on the 'E' button.
  - This will open another screen that will allow you to choose which error check type you would like from a list.
  - Multiple error check types can be selected by using the Ctrl or Shift keys on the keyboard.
  - Highlight the error check type you want from the displayed list and press the 'OK' button. You will be returned to the Error Tracking setup screen.
- Enter a valid value in the Valid Error Check ID (Vec ID) field.
  - Valid values for this field are between 001 and 999.
  - Note: Leading zeros must be entered for numbers less than 3 digits in length.
- When you are satisfied with the criteria you have entered, press the 'Execute Query' button. If you would like to clear the criteria you have entered or to begin a new search, press the 'Clear Query' button.
  - If you do not provide any search criteria, or if you search only on protocol and center number portions of the Participant field, you will be prompted with a message that states "You are searching for a large data set, which may take some time to return. Are you sure this is OK?" If you would like to continue running the query, press the 'OK' button. If you would like to provide more search criteria to narrow the results, press the 'Cancel' button.
- The results of the query will be displayed below the criteria entry section of the screen.
  - The Open Errors section of the results displays all errors that have not been marked as unresolvable.
  - The Non-Open Errors section of the results displays all errors that have been queried by the DCC and are at Center status. Since more than one error can be grouped into a query or unresolvable comment, these are also referred to as groups.
    - Note: All queries are groups, but not all groups are queries.
- The following results are displayed in the Open Errors section (see Figure 10-44): Participant ID (Participant), Initials, Visit Number (Vnum), Form, Form Type, Visit Date (Vdate), Record (Rec), Error, Primary Field (QPF), Original Value (Orig.), Days, Select, and Error Message.
  - The results are sorted by Participant ID (Protocol Number, Center Number and Participant Number), Visit Number, Form Name, Form Type, Visit Date, Error Check Type, and Valid Error Check ID.
  - Only entry errors for forms that have not yet been logged at the DCC and were first entered by a Center user should be displayed in the results.
  - The Days column keeps track of the number of days an error has been at a particular status. Once the status is changed and the group is saved, the Days field should be reset to 0. In the case of Open errors, this field displays the number of days since the error was inserted into the database.
  - The Error Message box will be populated when a row is highlighted and clicked on.

- The following results are displayed in the Non-Open Errors section (see Figure 10-44): Edit link, Participant, Initials, Group #, Visit Number (Vnum), Form, Comment, Days, and Status.
  - The results are sorted by ascending Participant ID (Protocol Number, Center Number, and Participant Number) and descending Group Number.
  - Some queries may contain multiple errors. The error displayed on the query screen is considered the primary error for that query group.
  - If any individual error within a group meets the criteria entered on the setup screen, that group should be displayed in the results section. This is also the case if the group's primary error does not match the criteria entered.
  - Only errors at Center status will be displayed.

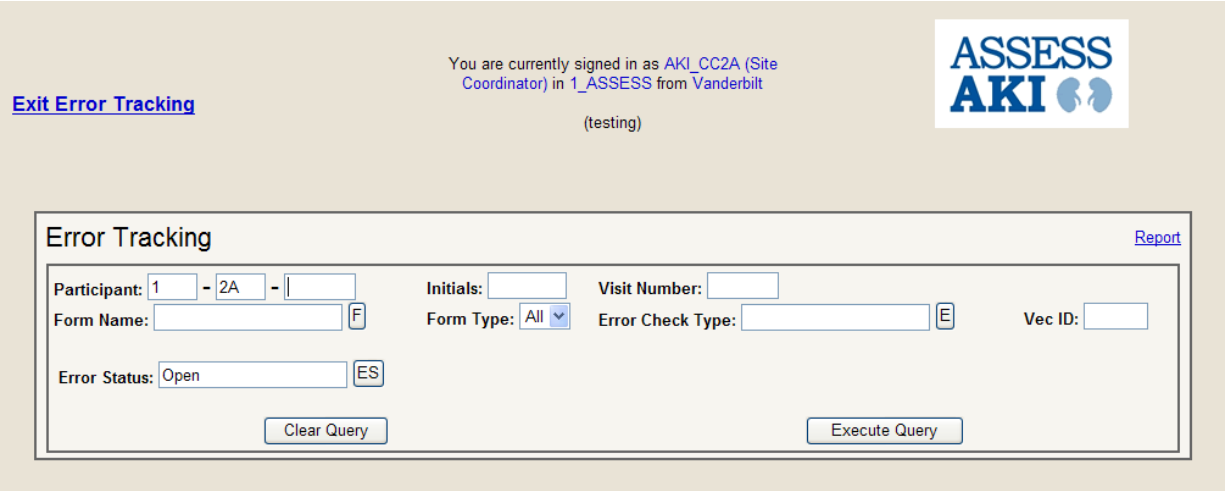


Figure 10-43

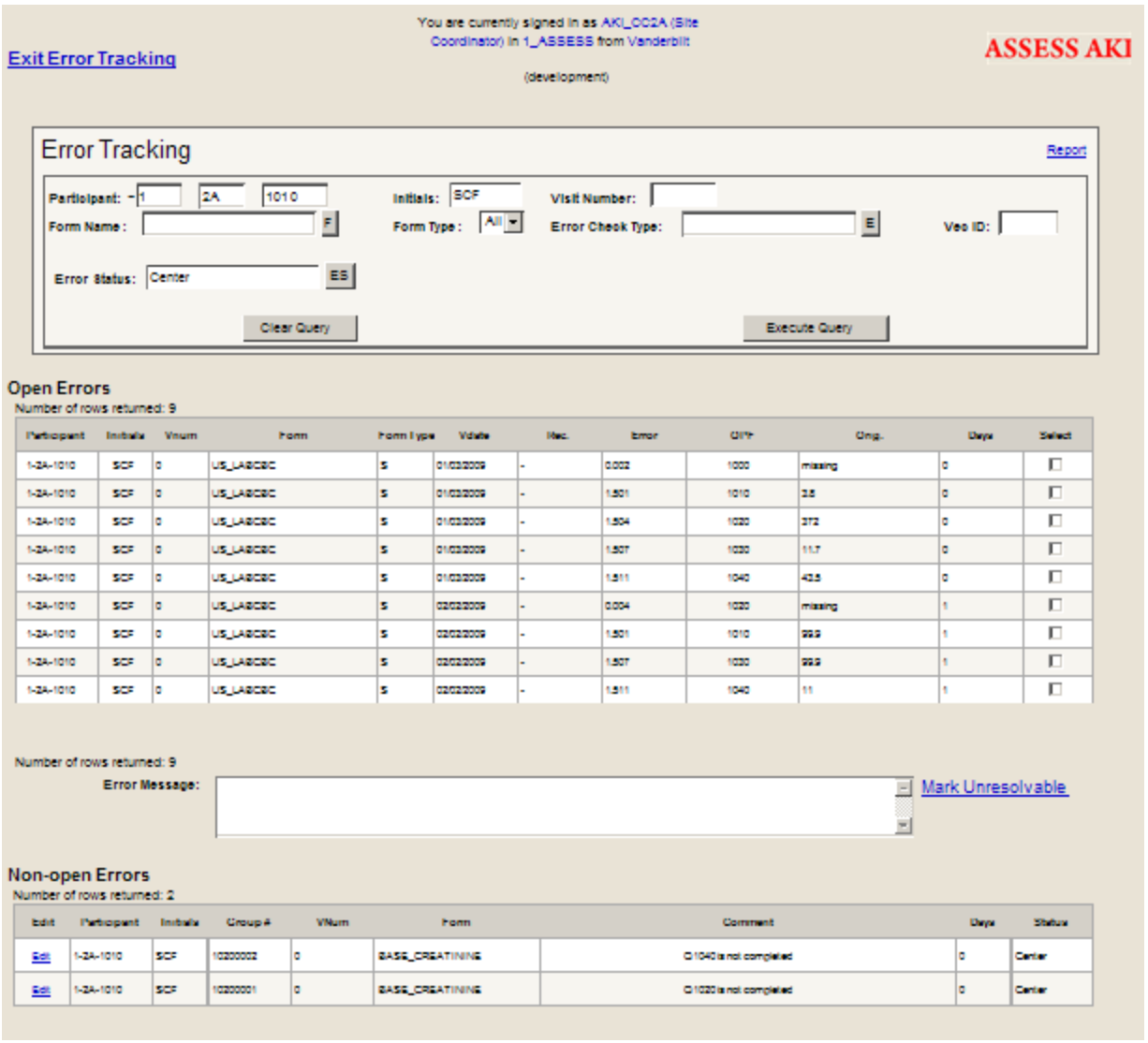


Figure 10-44

In order to mark errors unresolvable:

- Note: Only errors for the same participant, form name and visit number can be marked unresolvable at the same time. If you try to mark multiple errors from different form names or visit numbers as unresolvable, you will receive a pop up message that states, "You cannot create an unresolvable group if the errors are not all on the same form at the same visit. Please correct the error to continue." Once you press the 'OK' button, the selected errors will clear out and you will need to reselect the errors.
- Execute a query by following the steps above.
- Click the Select checkbox for one or multiple errors in the Open Errors section of the screen.
- Click the 'Mark Unresolvable' link next to the Error Message field.
- The Create an Unresolvable Error Group screen (see Figure 10-45) will display.

- There is a link to the Data Corrections module in the event that you need to perform other functions prior to marking the errors as unresolvable.
- Each error in the group will be displayed in a table with the following information: Remove link, Visit Number (Vnum), Form Name (Form), Form Type, Visit Date (Vdate), Record ID (Rec.), Error, Primary Field (QPF), Original Value (Orig.), and Corrected Value (Corr.).
- The Error Status field will be set to 'Closed'.
- If you need to remove any errors to the group, you can do so any time prior to saving the group by clicking the 'Remove' link next to the error(s) you do not want included in the group.
- Add a comment about the errors in the Add a comment field.
- The Corr. field will remain blank. You will not be able to add a value.
- If you would like to exit the screen without creating an unresolvable error group, press the 'Cancel' button and you will be returned to the Error Tracking screen.
- To save the group, press the 'Save' button and you will be returned to the Error Tracking setup screen. Your search will automatically re-execute and the errors that were saved will no longer appear in the open errors result.

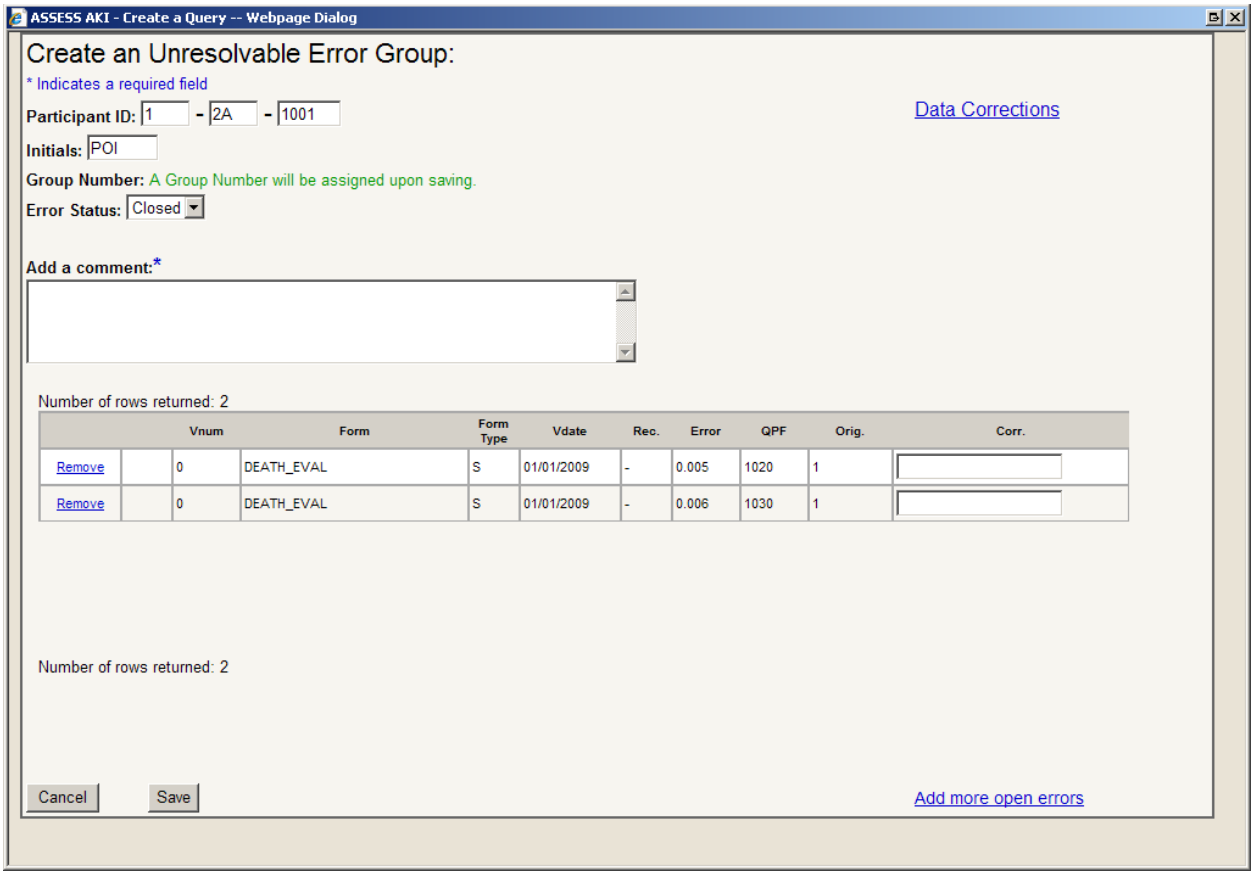


Figure 10-45

In order to edit a non-open row:

- Execute a query on a participant by following the steps above.
- Locate the query group you would like to modify and press the 'Edit' link.
- The Edit an Error Group screen (see Figure 10-46) will open in another window.
- Site Coordinators can only change the status from Center to DCC.
- The following fields are editable: Error Status, Add a comment, and Corrected Value (Corr.).
- There is a link to the Data Corrections module in the event that you need to perform other functions prior to making changes to the errors.

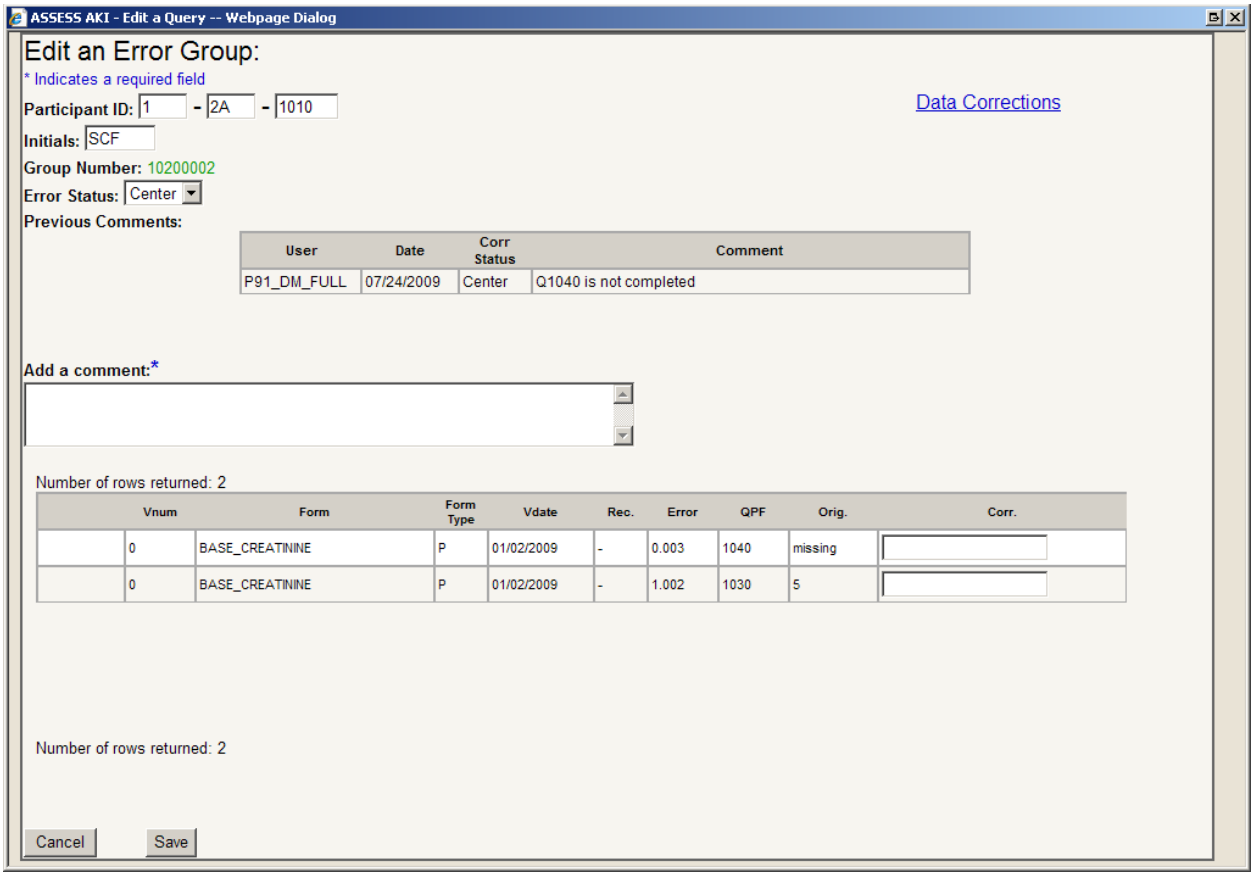


Figure 10-46

In order to view the Error Tracking Report:

- Click on the 'Error Tracking' link under the Editing heading of the Main Menu.
- Press the 'Report' link on the Error Tracking setup screen.
- The Error Tracking Report will open in another Internet browser window.
- Select the protocol you would like to search on from the Choose a Protocol drop-down.

- Press the 'Proceed' button.
- Select the error status you would like to search on by clicking the Status drop-down and choosing the desired value from the list.
- Press the 'Proceed' button.
- A list of participants that have queries with the status you specified on the previous screen will be displayed.
- Select which participant information you would like to view by clicking on the checkbox next to the Participant ID and Initials or click the checkbox next to Select All if you would like to view all of the participant information available.
- Press the 'Run Report' button.
- The following information is displayed on the report (see Figure 10-47): Query Number, Participant, Initials, Status, Visit Number, Visit Date, Form Name, Form Type, Record ID, Primary Field, Error Number, Original Value, Corrected Value, Date of Comment, User, and Comment.

ASSESS AKI - Error Tracking Report

Status: HOLD,DCC,CENTER,CLOSED

Current as of: 07/24/2009

Data Error Information

Query Number: 10200002
Participant: 1-2A-1010
Initials: SCF
Status: Center

Visit Number:	Visit Date:	Form Name:	Form Type:	Record ID:	Primary Field:	Error Number:	Original Value:	Corrected Value:
0	01/02/2009	BASE_CREATININE	P	-	1040	0.003	missing	
0	01/02/2009	BASE_CREATININE	P	-	1030	1.002	5	

Data Error Comments

Date of Comment:	User:	Comment:
07/24/2009	P91_DM_FULL	Q1040 is not completed

Data Error Information

Query Number: 10200001
Participant: 1-2A-1010
Initials: SCF
Status: Center

Visit Number:	Visit Date:	Form Name:	Form Type:	Record ID:	Primary Field:	Error Number:	Original Value:	Corrected Value:
0	01/02/2009	BASE_CREATININE	P	-	1020	0.001	missing	
0	01/02/2009	BASE_CREATININE	P	-	1030	0.002	missing	

Data Error Comments

Date of Comment:	User:	Comment:
07/24/2009	P91_DM_FULL	Q1020 is not completed

Exit Error Tracking Report

Figure 10-47

11 DATA COLLECTION, DATA ENTRY, AND DATA QUALITY CONTROL

11.A Data Collection

11.A.1 Distribution and Location of Forms

Each Clinical Research Center will print its own data collection forms, administrative forms, reference cards, and logs for each study from the private portion of the ASSESS-AKI website. Visit Packets will include a Visit Procedure Checklist followed by the corresponding visit-specific data collection packet forms. Visit packets will print in the order in which the forms should be administered.

Once logged into the ASSESS-AKI secure website, forms can be viewed and printed by choosing the Protocols link from the navigation bar. Forms are listed under the following categories: Adult and Pediatric. Once you choose a category, you will be able to choose the specific type of form, if applicable (i.e., Admin forms, Reference Cards, Visit Packets), or have the option to view all of the Individual data collection forms associated with the protocol.

The coordinators will have the option of pre-filling header information for the packet prior to printing. A quick reference document has been posted in both the adult and pediatric visit packets section within the Protocols: Forms: section.
The DCC recommends that each Clinical Research Center print extra copies of each visit packet, single form and handout as a backup in the event that Internet connections are unstable.

11.A.2 Participant Study Files

The Research Coordinator should create and maintain a study file for each participant. Many clinics find three-ring binders to be efficient study files. The study file, which should only be labeled to identify the protocol name, Participant ID number and participant initials, should contain all study materials, except the Registry (REGISTRY), Contact Information (P1_CONTACT/P2_CONTACT), Informed Consent, and Social Security Number (SSN) forms related to the participant. The files should be organized and stored sequentially by participant ID number. Within a participant file, all participant related data, reports, and correspondence should be organized by visit.

In order to ensure that PII is not stored with the participant files, please place all CONTACT forms in a binder. All REGISTRY forms should be placed in the Registry binder along with the Registry reports. All Informed Consents should also be placed in a separate binder.

The files should be organized and stored sequentially by participant ID number or participant initials. Within a participant file, all participant related data, reports, and correspondence should be organized by visit.

Please organize this information in the following order within a visit:

1. Visit Packet - forms ordered according to the visit procedure checklist
2. Reports such as, ECG and lab reports
3. Single Forms
4. Queries (optional)

5. Data Corrections (optional)

The Participant Visit Schedule should be placed in the front of the participant study file before any of the visit packets.

11.A.3 Participant ID Number, Subject Initials, and Coordinator/Technician ID

The participant ID number is assigned when an individual is approached at the first ASSESS-AKI study contact. To assign a participant ID number, select the next available blank entry on the appropriate Case or Control Participant Assignment Log (CASE/CTRL_PART_ASSIGN). This will be the primary participant identifier used during the study.

- The participant ID number is comprised of three sections divided by hyphens.
  - The first section signifies the protocol number (1=ASSESS- AKI – Adult, 2=ASSESS-AKI – Pediatric)
  - The second section identifies the Clinical Research Center (Yale – Cincinnati = 1B, Yale-Ontario = 1C, Yale-Montreal = 1D, Yale-New Haven = 1E, Vanderbilt = 2A, Kaiser - Oakland = 3A, Kaiser – San Francisco = 3B, Kaiser – Walnut Creek = 3C, Kaiser – Hayward = 3E, UW - Harborview = 4A)
  - The third section signifies the participant identifier within that Clinical Research Center (AKI participants will begin with 1001 and Non-AKI participants will begin with 5000)

  For example, an adult control participant ID at the Vanderbilt Center would be 1-2A-5025.

- The Case or Control Participant Assignment Log (CASE/CTRL_PART_ASSIGN) for each study must be kept by each CRC indefinitely. These logs will be reviewed at site visits.
- The participant's initials will be used as a secondary identifier. All participants must have at least three initials. The letter "X" should be used if the participant does not have a middle initial. The participant's initials may be changed during the duration of the ASSESS-AKI; however they will need to be updated in the ASSESS-AKI Registry. Please refer to Section 12 of the MOP for more information on changing the participant's initials.
- The Research Coordinator ID number will begin with the assigned center number and will be followed by four digits. The four digits may be the last four digits of the Research Coordinator's Social Security Number (or Social Insurance Number) or Employee ID, or four digits that the coordinator will remember. The alphabetic characters are dropped from the center ID number.

11.A.4 Completion of Forms

- If a form is participant/guardian completed, review the form instructions with the participant/guardian and emphasize legibility. Additionally, be available for questions while the participant/guardian is completing the form. The form will contain a Research Coordinator section at the end of the form to identify who completed the form/questionnaire.
- The method of form completion must remain consistent throughout the participant's ASSESS-AKI visit.

- Select responses to questions by placing an 'X' in the appropriate box. All forms should be completed using black or blue ink. If a box is incorrectly checked, with red ink, cross it out using a single line through the middle, place an 'X' in the correct box, initial, date, and circle the correct answer.
- Print all responses and make sure they are legible. For any open-ended question or comment, print the response clearly and restrict it to the space provided.
- Record dates using two digits for the month (i.e., 01, 03, 12), two digits for the day (i.e., 02, 31), and four digits for the year (i.e., 1941, 1996, 2002). The only exception is in the header section of the data collection forms, where dates will be recorded using two digit years.
- Use the comments section at the bottom of the form (Q6000) for notes to explain or clarify missing answers or unusual circumstances. Do NOT write any extraneous notes in the question response areas or in the margins.

11.A.5 Review of Completed Forms

All forms should be reviewed for legibility, accuracy, and completeness before the study visit/contact is complete so that any additional information or clarification can be obtained. Once the participant leaves a visit, any participant-completed data cannot be changed or updated by the Research Coordinator. If the participant is still present and a form is found to be completed incorrectly or is illegible, the participant should transcribe the information to another copy of the form. If recopying is necessary, carefully review the form instructions with the participant. Retain the original form in the Participant Study File for documentation purposes.

When making changes to answers or correcting mistakes, put a single line through the middle of the incorrect information, record the correct information using red ink, and initial and date the correct answer. For the sake of clarity, circle the correct response.

11.B Data Processing and Data Entry

11.B.1 Data Processing Cover Sheet (DPCS)

The Data Processing Cover Sheet (DPCS) facilitates the tracking of all data collection forms from the time of collection at the Clinical Research Center to the final processing at the DCC. The Research Coordinator should complete the top portion of this cover sheet by signing off on the following activities:

- review of completed forms
- registration and first data entry
- review and resolution of entry errors
- copying, collating, and preparing for delivery to the DCC

When preparing copies of the DPCS, be sure to use an original document printed from the website. Photocopies should not be made from another photo copied DPCS. The print quality of the DPCS is important because the DCC will be scanning all forms for electronic archival.

11.B.2 Data Entry Preparation

To prepare a packet or single form for data entry, the Research Coordinator should complete the participant ID number, participant initials, visit number, visit date (Single Form Only) and the form type at the top of the DPCS. The forms should be reviewed and collated according to the guidelines below:

- The original data collection forms should be sent to the DCC and photocopies will be stored at each Clinical Research Center.
- The Research Coordinator should review the packet/form again to ensure that all forms are completed accurately and legibly.
- When making changes to responses or correcting mistakes on incorrectly recorded information always use red ink. Put a single line through the middle of the incorrect information. Record the correct information and initial, date, and circle the correct answer. The forms are source documents. All changes to the data must be made to all copies of the forms.
- The person who reviewed the forms should record the current date and his/her ID number on the DPCS.

After reviewing, entering the forms, and resolving entry errors, the Research Coordinator should photocopy the forms. The originals should be sent to the DCC and the copies should be kept in the participant's folder at the Clinical Research Center. If a center is required to keep the originals, they should contact the DCC to discuss the matter. Note: Copies of forms should be made only after all changes have been made to the forms.

Forms with instructions "FOR USE ONLY AT THE CLINICAL RESEARCH CENTER - DO NOT FORWARD TO DCC" should be filed in the participant study file and not forwarded to the DCC.

The data sent to the DCC should be paper-clipped or binder-clipped and organized in the order listed below.

Packet Forms

1. Data Processing Cover Sheet
2. Visit Procedure Checklist
3. Packet Forms - forms ordered according to the visit procedure checklist
4. Original copy of required report(s)

Single Forms

1. Data Processing Cover Sheet
2. Single Form

The person collating forms should record the current date and his/her ID number on the Data Processing Cover Sheet (DPCS).

11.B.3 Data Shipment Preparation

The forms should be packaged and mailed to the DCC once a week via an overnight or two-day mail service with tracking capabilities according to the following schedule.

Clinical Research Center	Day of the Week to Mail Forms to the DCC
Yale – Cincinnati	Tuesday
Yale – Ontario	Wednesday
Yale – Montreal	Thursday
Yale – New Haven	Friday
Vanderbilt	Monday
Kaiser - Oakland	Tuesday
Kaiser – San Francisco	Thursday
Kaiser – Walnut Creek	Friday
Kaiser - Hayward	Friday
U Washington	Tuesday

If for some reason a Clinical Research Center does not mail any forms during a given week, the Research Coordinator should notify a member of the data management group at the DCC indicating that no data forms will be sent that week.

For sites that ship V0 and V3M packets together, V0 and V3M packet are to be received by the DCC within 14 days of V3M. V0 and V3M single forms are to be received by the DCC within 14 days from the date of completion.

For sites that ship V0 and V3M packets separately, visit packets are to be received by the DCC within 14 days of the visit date.

After V3M, all visit packets are to be received by the DCC within 14 days of the visit date.

Withdrawal forms should be data entered as soon as possible and the visit packets for ineligible participants are to be received by the DCC within 14 days from data entry of the Withdrawal (WITHDR) form.

After entry errors are resolved, data collected should be sent to the DCC. Forms must be double-wrapped by packaging them in a sealed envelope within the appropriate FEDEX envelope or box. It is very important that the data is sent to the DCC within one week of resolution of entry errors so that the database entries can be quickly verified at the DCC and additional errors can be identified.

If the data is not received on schedule, the Primary Data Manager will follow up with the Research Coordinator. Routine tardiness in forms arrival at the DCC will be brought to the attention of the Scientific Coordinator and/or the Principal Investigator at the DCC.

All forms and correspondence related to study forms and procedures should be sent to the Primary Data

Manager.

If packets/forms are repeatedly received at the DCC in a condition that is unsuitable for processing (multi-page forms are stapled, packets are not properly ordered and paper clipped, Data Processing Cover Sheet is not properly completed, etc.), they may be returned to the Clinical Research Center for resolution. If this continues to be a persistent problem, it will be brought to the attention of the Scientific Coordinator and/or the Principal Investigator at the DCC.

11.C Data Quality Control: Queries

11.C.1 Generation of Errors

Once the forms have been processed at the DCC, additional computer error checking will be performed to identify problem data. Unresolved errors from first entry are checked again followed by additional checks only done at the DCC. The DCC checks include:

- Checks for missing data, missing forms, and missing packets.
- Checks for out-of-range values and certification checks. All responses will be compared to a pre-determined range of possible values.
- Logical checks will be performed for consistency in participant responses within and between forms as well as within and between visits.

11.C.2 Queries

If a Data Manager cannot resolve problem data identified by the checks described above, a query requesting resolution of the problem will be sent to the Research Coordinator. The Research Coordinator can view and respond to queries through the Error Tracking module in the data entry application. A query may contain one error or multiple errors and will provide a description of the problem. Each error will identify the field requiring resolution. The Research Coordinator can provide a corrected value for each error and inform the DCC of the change. See Section 10 of the ASSESS- AKI MOP for more information regarding this procedure.

There are several things to note when resolving queries:

- The Research Coordinator should respond to queries within five working days of receipt.
- Printing individual queries is optional. If the Research Coordinator chooses to print queries for documentation, please file them in the appropriate participant visit file. See Section 10 of the ASSESS-AKI MOP for more information regarding printing queries.
- Always use red ink when making changes to the participant data as a result of queries or clinic initiated Data Corrections. Put a single line through the middle of the incorrect information. Record the correct information, initial, date and circle the correct answer. Data Corrections should be filed in the appropriate participant visit file if printed.
- Once queries are returned to the DCC, the Data Manager will use the correct values to update the data in the ASSESS-AKI Data Management System. If the Data Manager requires further clarification, he or she will send the query back to the Research Coordinator.

If a Research Coordinator is delinquent in answering queries, follow up measures will be taken by the DCC to retrieve the necessary information. A phone call or email will be sent to the clinic if a query has not been resolved within 14 days of receipt. A second phone call or email will be sent if a total of 28 days has passed without resolution. If delinquent queries become a persistent problem at a particular Clinical Research Center, it will be brought to the attention of the Scientific Coordinator and/or the Principal Investigator at the DCC.

11.D Data Processing and Quality Reports

The quality reports are located on the secure website.

The reports characterize the clinical Research Center data entry and submission timeliness with the following report types:

Average number of days between visit date and data entry, average number of days between data entry and data collection form arrival at the DCC, total number of queries sent from the DCC to the CRC, total number of queries currently at CRC status, average number of days between the date a query is sent to the CRC and the CRC's initial response, number of overdue queries, and average number of days between data collection form arrival at the DCC and verification by the DCC.

11.E Participant Accrual Reports

The accrual reports are located on the secure website.

The reports characterize participant accrual with the following report types:

AKI participant /non-AKI participant summary reports on Age categories, Gender, Location, Primary Race, AKI participant/non-AKI participant summary status, enrollment, ineligible reasons, withdrawal reasons, Visit 0 and Visit 3M summary, severity

11.F Confidentiality

- It is imperative that the DCC remain blinded to the names, addresses, social security numbers, and other confidential identifiers regarding any participant in an ASSESS-AKI study. Although the DCC will audit this information during data site visits at each clinic, confidential data must never be sent to the DCC.
- Participant confidentiality can be maintained by always labeling reports, forms, queries and any other correspondence with the Participant's ID and initials instead of his/her name.
- Ideally, study personnel should refrain from speaking a participant's full name during study visits or in general conversation. When an individual's name must be spoken, stating his/her first name only is preferred.
- All data must be kept under lock and key on a daily basis. Only study personnel should have access to the data.
- Keys to locked data should be limited to the fewest number of personnel possible.

See Section 5 of the ASSESS-AKI MOP for more information regarding confidentiality.

12 REGISTRY

12.A Introduction

The ASSESS-AKI Registry has been established to store basic demographic data for individuals screened by the Research Coordinator for potential enrollment in an ASSESS-AKI study. Demographic information collected for the ASSESS-AKI Registry is limited to gender, racial/ethnic categories, and date of birth. Storing data for all screened individuals in one registry allows the DCC to report to the National Institutes of Health (NIH) the demographics of all participants screened over the life of the grant.
The Registry facilitates tracking participants through their participation in multiple protocols via the generation of a master identification number. Working in the context of a registry also avoids duplication of data collection for immutable demographic information.

This section describes the Registry and related Clinical Research Center procedures.

12.B Clinical Research Center Process

12.B.1 Obtain Consent/HIPPA Authorization

Before obtaining any personal information from the participant for the Registry, he or she must read and sign an IRB-approved ASSESS-AKI protocol consent form and if necessary, an institutional HIPAA authorization form. The protocol consent document must contain an ASSESS-AKI-approved description of the Registry, its contents, and the longevity of the data that are collected. The HIPAA authorization form must list the ASSESS-AKI DCC as a recipient of Personally Identifiable Information (PII) and must indicate that there is no deadline for use and disclosure of the participant's PII. Language regarding the Registry must be embedded in each and every protocol consent/HIPAA authorization document.

Participants must agree to have their demographic data present in the ASSESS-AKI Registry indefinitely or they may not participate in any ASSESS-AKI studies. Once a participant consents to include his or her data in the Registry, it cannot be removed, even if the participant revokes his or her consent in the future.

After a participant has signed both the informed consent document and if necessary, the HIPAA authorization form, the Research Coordinator may collect and record information for the Registry as outlined in the following steps.

12.B.2 Complete Registry Data Collection Form

The first page of the Registry (REGISTRY) form should be completed by the Research Coordinator, this information should not be asked of the participant.
Participants who are older than 89 years are NOT eligible for entry into the ASSESS-AKI registry.
Participants who are between 18 and 89 years old must be able to provide consent or have a surrogate present to provide consent to be eligible for entry into the ASSESS-AKI Registry.

Q1030 If surrogate consent is provided, the type of surrogate must be recorded on the Registry form. The type of surrogate is not data entered into the ASSESS-AKI registry.

Q1070 If the participant is less than 7 years old, answer N/A.

The second page of the Registry (REGISTRY) form may be completed by the participant; however the Research Coordinator is required to review the information on this page for completeness.

Q1090 For the Ontario Site only: The number 15 should be entered for the day of the participant's date of birth.

Race and Ethnicity

Q1110-Q1160 The participant should check 'Yes' or 'No' for each racial category. The participant may answer 'Yes' to more than one category. If Q1160 is answered 'Yes' a description must be provided on the form.

Definitions of ethnic backgrounds:

1. American Indian or Alaskan Native: A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition.
2. Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for examples, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Cambodia, Thailand, and Vietnam.
3. Black or African American: A person having origins in any of the black racial groups of Africa.
4. White: A person having origins in any of the original people of Europe, North Africa, or Middle East.
5. Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

Q1170 The participant must choose a primary racial category that best describes him/her. If the participant is of mixed race and cannot commit to one primary racial background provided in Q1170, 'More Than One Race' may be selected. The use of 'More Than One Race' in Q1170 requires more than one racial category to be answered 'Yes' within Q1110-Q1150 or Q1160 must be answered 'Yes'. If the participant marked Q1160, specified the race, and refused to choose a primary race, the Research Coordinator may mark the appropriate racial category for Q1170 based on the response to Q1160. For example, if the participant marked Q1160 as 'Yes,' specified race to be Portuguese, and refused to answer Q1170, the Research Coordinator may mark Q1170 as 'White' based on the definitions provided above.

12.B.3 Search Registry

Before entering the Registry (REGISTRY) form, the Research Coordinator should enter the participant's initials (real or scrambled), date of birth, and gender into the Registry search application. The application determines if anyone was registered Consortium-wide in the past with similar data. If potential matches on initials, date of birth, and gender are found, the relevant master ID numbers are listed on the screen, along with their associated links (i.e., protocol IDs) from previous ASSESS-AKI participation, if any, and all search criteria. Additional information such as the Clinical Research Center at which the participant was last enrolled is provided in the results section. All potential matches from the Clinical Research Center should be reviewed to decipher if the participant has already been assigned a Master ID in the ASSESS-AKI

registry. This may be confirmed by referencing the participant assignment log(s). If a match is confirmed, the registry form should be compared to the original registry form to review and discrepancies.
If the participant has already been assigned a Master ID, registration is not required and the research coordinator may proceed to the protocol enrollment module within the data entry application. Note: The entry of the Master ID, initials, date of birth, and gender will be required for protocol enrollment. A registry report may be printed from the application to facilitate protocol enrollment procedures.
If no matches are identified after searching for an individual's demographic information in the Registry, then the participant is new to the ASSESS-AKI Consortium and a record must be established in the Registry for him or her. The Research Coordinator should proceed with entry of the Registry (REGISTRY) form.

12.B.4 Enter New Participant

After the Registry (REGISTRY) form is complete, data should be entered into the ASSESS-AKI Data Management System. Specific instructions for accessing and interacting with the Registry module are located in the ASSESS-AKI Data Management System User Manual. This system requires that all data on the Registry (REGISTRY) form be entered twice (by the same individual) to ensure accuracy.

Once a participant is completely registered into the system (i.e., Registry status complete) and a master ID number has been assigned, his or her record is considered final and may not be altered by the Clinical Research Center in the future.

Date of birth and gender generally may not be altered, unless a data entry error occurred when the participant's data were entered into the Registry. If an entry error occurred, the DCC must be notified and a Registry Data Correction (REG_CORRECT) form filed immediately following the Registry process. The DCC should be contacted for assistance for any other situations where updates to the participant's demographic data are requested. Depending on the request, the DCC reserves the right to deny specific requests for changes.

12.B.5 Print Registry Report

Once you have completed the registry data entry a pre-filled registry summary report will appear. The Registry summary report should be printed and the participant's first and last name should be written on the report. This registry summary report should not be sent to the DCC. Because Registry (REGISTRY) form and summary report contain the names of study participants, they should never be sent to the DCC. Sending these forms to the DCC constitutes a breach of confidentiality that warrants assignment of a protocol violation.

12.B.6 File Materials

Completed original Registry (REGISTRY) forms and summary reports should be stored in an ASSESS-AKI Registry binder alphabetically by the participant's last name.

Because the Registry summary reports contain critical information regarding the link between a Master ID number and the participant who belongs to it, the binder should be kept in locked filing cabinets accessible only by authorized ASSESS-AKI Research Coordinators.

12.C Registry Audits

12.C.1 Site Visit Audits

Formal data audits initiated by the DCC will include a thorough review of the Clinical Research Center's Registry materials. The DCC will check for the presence of specific Registry forms/reports, completeness of the forms, presence of source documentation, and appropriate storage of Registry items.

12.D Registry Data Collections

The Registry Data Correction form contains a list of primary fields, with space available to complete the original values and corrected values. For every field that requires a correction, record the incorrect value in the original value field, and record the correct value in the corrected value field. Leave the original value and corrected value fields blank for all fields that do not require a correction. Provide a reason for the corrections needed in the space provided.

Fax the REG_CORRECT form to the ASSESS-AKI Scientific Coordinator.

12.E Transfer of Participants from one ASSESS-AKI Center to Another

It is possible that a given participant might relocate from one Clinical Research Center to another over the duration of the ASSESS-AKI grant. For example, a participant who originated at the ASSESS-AKI Yale Chicago site may have enrolled in a protocol and then may move to a location close to the Yale Cincinnati site. If this individual chooses to continue to participate in the ASSESS-AKI protocol as a participant at the Yale Cincinnati site, he or she should maintain the master ID number that was previously assigned at Yale Chicago. The participant should NOT be re-registered under a new master ID number. The Yale Cincinnati Research Coordinator should contact the Yale Chicago Research Coordinator to obtain a copy of the participant's Registry (REGISTRY) form, search the Registry to verify the participant's demographic information and previous protocol ID links, and generate a registry summary report. Once the participant's master ID number has been confirmed, the Registry form and report should be stored in the Yale Cincinnati site's Registry binder. The original Clinical Research Center, in this case Yale Chicago, should retain the original Registry (REGISTRY) form. Both Clinical Research Centers are responsible for audits of the participant's Registry materials, as outlined above.

13 MOP DESCRIPTIONS

The most recent version of each MOP should be on file at each site as well as all of the MOP-specific update memos.

13.A Biospecimen MOP

This MOP includes the collection, processing, and shipping instructions and data collection forms specific to the inpatient and outpatient Biospecimen collection for the Adult (P1) and Pediatric (P2) ASSESS AKI protocols. It includes information about the NIDDK Biorepository (Precision for Medicine, Fisher, and Rutgers) and the Central Lab as well as a calendar of the holiday closures. Protocol details may be found in the Protocol MOP, not in the Biospecimen MOP.

- Section 1 is the Biospecimen collection at the Inpatient Adult Visit,
- Section 2 is the Biospecimen collection at the Outpatient Adult Visit,
- Section 3 is the Biospecimen collection at the Inpatient Pediatric Visit,
- Section 4 is the Biospecimen collection at the Outpatient Pediatric Visit, and
- Section 5 is the NIDDK Repository (Precision for Medicine)
- Section 6 is the NIDDK Repository (Fisher and Rutgers) and Central Lab.
- Section 7 is the Biospecimen processing for the SWAN Study.
- Section 8 is the Biospecimen processing for the CLANS Study.

13.B ECG MOP

This is the Electrocardiography Assessment Manual provided by the ASSESS-AKI Central ECG Reading Center, which is the Epidemiological Cardiology Research Center (EPICARE). It contains background information, field center procedures, and quality control issues and procedures for administering the ECG.

13.C Equipment MOP

This provides the features, functions, instructions, care and maintenance, error indicators, and supply information for the standard equipment that is used at the clinical research centers. These include:

- OMRON HEM-907,
- OMRON HEM-705CPN,
- OMRON BP785
- Dinamap GECarescape V100
- UC-321PL Precision Health Scale,
- Scaletronix
- Scale-tronix 4800 Pediatric Scale,

- Scale-tronix 4800 Infant Scale,
- TANITA 1583 Baby Scale,
- Bayer Clinitek Status Analyzer
- SECA 213 Stadiometer
- SECA 217 Stadiometer
- Perspective Enterprises Model No. PE-WM-60-84 Stadiometer, and
- Holtain Harpenden Stadiometer.
-

13.D Event Adjudication (EA) MOP

This MOP includes a review of the renal and cardiovascular outcomes, event investigations, event adjudications, adjudication criteria, and reviewer forms.

13.E General MOP

This MOP includes the protocol, administrative organization and role of participants, Consortium committees, NIDDK-appointed committees, standing policies and procedures, clinical research center standardization, recruitment, participant retention, computing and networking environment, study site data entry application, data collection, data entry, and data quality control, registry. This MOP may be referenced for general policies and procedures that are not specific to a protocol.

13.F Protocol MOP

This MOP is specific to the Adult (P1) and Pediatric (P2) ASSESS AKI protocols. Explanations, definitions, and examples related to procedures and completion of data collection forms are included. If more detailed information is available in another MOP, that MOP is referenced. This MOP does not include the collection, processing, and shipping instructions nor data collection forms specific to the inpatient and outpatient Biospecimen collection for the Adult (P1) and Pediatric (P2) ASSESS AKI protocols. It does not include the procedures related to any ancillary study.

13.G Quality of Life and Cognitive Function MOP

The QOL MOP provides the general instructions for administering:

- Modified Mini-Mental State Exam (3MS) and its telephone version,
- SF-12,
- TRAILS B, and
- PEDSQL.

14 Appendix A: Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Updated October 2001)

Publication Ethics: Sponsorship, Authorship, and Accountability:

International Committee of Medical Journal Editors (see end of text):

A small group of editors of general medical journals met informally in Vancouver, British Columbia, in 1978 to establish guidelines for the format of manuscripts submitted to their journals. The group became known as the Vancouver Group. Its requirements for manuscripts, including formats for bibliographic references developed by the National Library of Medicine, were first published in 1979. The Vancouver Group expanded and evolved into the International Committee of Medical Journal Editors (ICMJE), which meets annually; gradually it has broadened its concerns.

The committee has produced multiple editions of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Over the years, issues have arisen that go beyond manuscript preparation. Some of these issues are now covered in the Uniform Requirements; others are addressed in separate statements.

The entire Uniform Requirements document was revised in 1997. Sections were updated in May 1999 and May 2000. A major revision is scheduled for 2001. The total content of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals may be reproduced for educational, not-for-profit purposes without regard for copyright; the committee encourages distribution of the material.

Journals that agree to use the Uniform Requirements (over 500 do so) are asked to cite a version published in 1997 or later in their instructions to authors.

It is important to emphasize what these requirements do and do not imply.

First, the Uniform Requirements are instructions to authors on how to prepare manuscripts, not to editors on publication style. (But many journals have drawn on them for elements of their publication styles.)

Second, if authors prepare their manuscripts in the style specified in these requirements, editors of the participating journals will not return the manuscripts for changes in style before considering them for publication. In the publishing process, however, the journals may alter accepted manuscripts to conform with details of their publication style.

Third, authors sending manuscripts to a participating journal should not try to prepare them in accordance with the publication style of that journal but should follow the Uniform Requirements.

Authors must also follow the instructions to authors in the journal as to what topics are suitable for that journal and the types of papers that may be submitted-for example, original articles, reviews, or case reports. In addition, the journal's instructions are likely to contain other requirements unique to that journal, such as the number of copies of a manuscript that are required, acceptable languages, length of articles, and approved abbreviations.

Participating journals are expected to state in their instructions to authors that their requirements are in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals and to cite a published version.

Issues to Consider Before Submitting a Manuscript:

Redundant or Duplicate Publication:

Redundant or duplicate publication is publication of a paper that overlaps substantially with one already published.

Readers of primary source periodicals deserve to be able to trust that what they are reading is original unless there is a clear statement that the article is being republished by the choice of the author and editor. The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources.

Most journals do not wish to receive papers on work that has already been reported in large part in a published article or is contained in another paper that has been submitted or accepted for publication elsewhere, in print or in electronic media. This policy does not preclude the journal considering a paper that has been rejected by another journal, or a complete report that follows publication of a preliminary report, such as an abstract or poster displayed for colleagues at a professional meeting. Nor does it prevent journals considering a paper that has been presented at a scientific meeting but not published in full or that is being considered for publication in a proceedings or similar format. Press reports of scheduled meetings will not usually be regarded as breaches of this rule, but such reports should not be amplified by additional data or copies of tables and illustrations.

When submitting a paper, the author should always make a full statement to the editor about all submissions and previous reports that might be regarded as redundant or duplicate publication of the same or very similar work. The author should alert the editor if the work includes subjects about which a previous report has been published. Any such work should be referred to and referenced in the new paper. Copies of such material should be included with the submitted paper to help the editor decide how to handle the matter.

If redundant or duplicate publication is attempted or occurs without such notification, authors should expect editorial action to be taken. At the least, prompt rejection of the submitted manuscript should be expected. If the editor was not aware of the violations and the article has already been published, then a notice of redundant or duplicate publication will probably be published with or without the author's explanation or approval.

Preliminary reporting to public media, governmental agencies, or manufacturers, of scientific information described in a paper or a letter to the editor that has been accepted but not yet published violates the policies of many journals. Such reporting may be warranted when the paper or letter describes major therapeutic advances or public health hazards such as serious adverse effects of drugs, vaccines, other biological products, or medicinal devices, or reportable diseases. This reporting should not jeopardize publication, but should be discussed with and agreed upon by the editor in advance.

Acceptable Secondary Publication:

Secondary publication in the same or another language, especially in other countries, is justifiable, and can be beneficial, provided all of the following conditions are met.

1. The authors have received approval from the editors of both journals; the editor concerned with secondary publication must have a photocopy, reprint, or manuscript of the primary version.
2. The priority of the primary publication is respected by a publication interval of at least one week (unless specifically negotiated otherwise by both editors).
3. The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
4. The secondary version faithfully reflects the data and interpretations of the primary version.
5. The footnote on the title page of the secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part and states the primary reference. A suitable footnote might read: "This article is based on a study first reported in the [title of journal, with full reference]."

Permission for such secondary publication should be free of charge.

Protection of Patients' Rights to Privacy:

Patients have a right to privacy that should not be infringed without informed consent. Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that the patient be shown the manuscript to be published.

Identifying details should be omitted if they are not essential, but patient data should never be altered or falsified in an attempt to attain anonymity. Complete anonymity is difficult to achieve, and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of patients is inadequate protection of anonymity.

The requirement for informed consent should be included in the journal's instructions for authors. When informed consent has been obtained it should be indicated in the published article.

Reporting guidelines for specific study designs:

Research reports frequently omit important information. The general requirements listed in the next section relate to reporting essential elements for all study designs. Authors are encouraged in addition to consult reporting guidelines relevant to their specific research design. For reports of randomized controlled trials authors should refer to the CONSORT statement (http://www.consort-statement.org/). This guideline provides a set of recommendations comprising a list of items to report and a patient flow diagram.

Requirements for Submission of Manuscripts:

Summary of Technical Requirements:

Double space all parts of manuscripts. Begin each section or component on a new page. Review the sequence: title page, abstract and key words, text, acknowledgments, references, tables (each on separate page), legends. Illustrations, unmounted prints, should be no larger than 203 × 254 mm (8 × 10 inches). Include permission to reproduce previously published material or to use illustrations that may identify human subjects. Enclose transfer of copyright and other forms. Submit required number of paper copies. Keep copies of everything submitted.

Preparation of Manuscript:

The text of observational and experimental articles is usually (but not necessarily) divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections (especially the Results and Discussion sections) to clarify their content. Other types of articles, such as case reports, reviews, and editorials, are likely to need other formats. Authors should consult individual journals for further guidance.

Type or print out the manuscript on white bond paper, 216 × 279 mm (8.5 × 11 inches), or ISO A4 (212 × 297 mm), with margins of at least 25 mm (1 inch). Type or print on only one side of the paper. Use double spacing throughout, including for the title page, abstract, text, acknowledgments, references, individual tables, and legends. Number pages consecutively, beginning with the title page. Put the page number in the upper or lower right-hand corner of each page.

Manuscripts on Disks:

For papers that are close to final acceptance, some journals require authors to provide a copy in electronic form (on a disk); they may accept a variety of word-processing formats or text (ASCII) files.

When submitting disks, authors should:

1. Be certain to include a print-out of the version of the article that is on the disk;
2. Put only the latest version of the manuscript on the disk;
3. Name the file clearly;
4. Label the disk with the format of the file and the file name;
5. Provide information on the hardware and software used.

Authors should consult the journal's instructions to authors for acceptable formats, conventions for naming files, number of copies to be submitted, and other details.

Title Page:

The title page should carry 1) the title of the article, which should be concise but informative; 2) the name by which each author is known, with his or her highest academic degree(s) and institutional affiliation; 3) the name of the department(s) and institution(s) to which the work should be attributed; 4) disclaimers, if any; 5) the name and address of the author responsible for correspondence about the manuscript; 6) the name and address of the author to whom requests for reprints should be addressed or a statement that reprints will not be available from the authors; 7) source(s) of support in the form of grants, equipment, drugs, or all of these; and 8) a short running head or footline of no more than 40 characters (count letters and spaces) at the foot of the title page.

Authorship:

All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article.

Authorship credit should be based only on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Conditions 1, 2, and 3 must all be met. Acquisition of funding, the collection of data, or general supervision of the research group, by themselves, do not justify authorship.

Authors should provide a description of what each contributed, and editors should publish that information. All others who contributed to the work who are not authors should be named in the Acknowledgments, and what they did should be described (see Acknowledgments).

Increasingly, authorship of multicenter trials is attributed to a group. All members of the group who are named as authors should fully meet the above criteria for authorship. Group members who do not meet these criteria should be listed, with their permission, in the Acknowledgments or in an appendix (see Acknowledgments).

The order of authorship on the byline should be a joint decision of the coauthors. Authors should be prepared to explain the order in which authors are listed.

Abstract and Key Words:

The second page should carry an abstract (of no more than 150 words for unstructured abstracts or 250 words for structured abstracts). The abstract should state the purposes of the study or investigation, basic procedures (selection of study subjects or laboratory animals; observational and analytical methods), main findings (giving specific data and their statistical significance, if possible), and the principal conclusions. It should emphasize new and important aspects of the study or observations.

Below the abstract authors should provide, and identify as such, 3 to 10 key words or short phrases that will assist indexers in cross-indexing the article and may be published with the abstract. Terms from the

Medical Subject Headings (MeSH) list of Index Medicus should be used; if suitable MeSH terms are not yet available for recently introduced terms, present terms may be used.

Introduction:

State the purpose of the article and summarize the rationale for the study or observation. Give only strictly pertinent references and do not include data or conclusions from the work being reported.

Methods:

Describe your selection of the observational or experimental subjects (patients or laboratory animals, including controls) clearly. Identify the age, sex, and other important characteristics of the subjects. Because the relevance of such variables as age, sex, and ethnicity to the object of research is not always clear, authors should explicitly justify them when they are included in a study report. The guiding principle should be clarity about how and why a study was done in a particular way. For example, authors should explain why only subjects of certain ages were included or why women were excluded. Authors should avoid terms such as "race," which lacks precise biological meaning, and use alternative descriptors such as "ethnicity" or "ethnic group" instead. Authors should specify carefully what the descriptors mean, and tell exactly how the data were collected (for example, what terms were used in survey forms, whether the data were self-reported or assigned by others, etc.).

Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration.

Reports of randomized clinical trials should present information on all major study elements, including the protocol (study population, interventions or exposures, outcomes, and the rationale for statistical analysis), assignment of interventions (methods of randomization, concealment of allocation to treatment groups), and the method of masking (blinding).

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

Ethics:

When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983. Do not use patients' names, initials, or hospital numbers, especially in illustrative material. When reporting experiments on animals, indicate whether the institution's or a national research council's guide for, or any national law on, the care and use of laboratory animals was followed.

Statistics:

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of P values, which fails to convey important quantitative information. Discuss the eligibility of experimental subjects. Give details about randomization. Describe the methods for and success of any blinding of observations. Report complications of treatment. Give numbers of observations. Report losses to observation (such as dropouts from a clinical trial). References for the design of the study and statistical methods should be to standard works when possible (with pages stated) rather than to papers in which the designs or methods were originally reported. Specify any general-use computer programs used.

Put a general description of methods in the Methods section. When data are summarized in the Results section, specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and “sample." Define statistical terms, abbreviations, and most symbols.

Results:

Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations.

Discussion:

Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by the data. In particular, authors should avoid making statements on economic benefits and costs unless their manuscript includes economic data and analyses. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

Acknowledgments:

List all contributors who do not meet the criteria for authorship, such as a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as "clinical investigators" or "participating investigators,"

and their function or contribution should be described for example, "served as scientific advisors," "critically reviewed the study proposal," "collected data," or "provided and cared for study patients."

Because readers may infer their endorsement of the data and conclusions, all persons must have given written permission to be acknowledged.

References:

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure.

Use the style of the examples below, which are based on the formats used by the NLM in Index Medicus. The titles of journals should be abbreviated according to the style used in Index Medicus. Consult the List of Journals Indexed in Index Medicus, published annually as a separate publication by the library and as a list in the January issue of Index Medicus. The list can also be obtained through the library's web site (http://www.nlm.nih.gov/).

Avoid using abstracts as references. References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication.

The references must be verified by the author(s) against the original documents.

The Uniform Requirements style (the Vancouver style) is based largely on an ANSI standard style adapted by the NLM for its databases. Notes have been added where Vancouver style differs from the style now used by NLM.

Articles in Journals :

1. Standard journal article

List the first six authors followed by et al.
(Note: NLM now lists up through 25 authors; if there are more than 25 authors, NLM lists the first 24, then the last author, then et al.)

Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996 Jun 1;124 (11):980-3.

As an option, if a journal carries continuous pagination throughout a volume (as man y medical journals do) the month and issue number may be omitted.

(Note: For consistency, the option is used throughout the examples in Uniform Requirements. NLM does not use the option.)
Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996;124:980-3.

More than six authors:
Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996;73:1006- 12.

2. Organization as author

The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164: 282-4.

3. No author given

Cancer in South Africa [editorial]. S Afr Med J 1994;84:15.

4. Article not in English

(Note: NLM translates the title to English, encloses the translation in square brackets, and adds an abbreviated language designator.)
Ryder TE, Haukeland EA, Solhaug JH. Bilateral infrapatellar seneruptur hostidligere frisk kvinne. Tidsskr Nor Laegeforen 1996;116:41-2.

5. Volume with supplement

Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect 1994;102 Suppl 1:275-82.

6. Issue with supplement

Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. Semin Oncol 1996;23(1 Suppl 2):89-97.

7. Volume with part

Ozben T, Nacitarhan S, Tuncer N. Plasma and urine sialic acid in non-insulin dependent diabetes mellitus. Ann Clin Biochem 1995;32(Pt 3):303-6.

8. Issue with part

Poole GH, Mills SM. One hundred consecutive cases of flap lacerations of the leg in ageing patients. N Z Med J 1994;107(986 Pt 1):377-8.

9. Issue with no volume

Turan I, Wredmark T, Fellander-Tsai L. Arthroscopic ankle arthrodesis in rheumatoid arthritis. Clin Orthop 1995;(320):110-4.

10. No issue or volume

Browell DA, Lennard TW. Immunologic status of the cancer patient and the effects of blood transfusion on antitumor responses. Curr Opin Gen Surg 1993:325-33.

11. Pagination in Roman numerals

Fisher GA, Sikic BI. Drug resistance in clinical oncology and hematology. Introduction. Hematol Oncol Clin North Am 1995 Apr;9(2):xi-xii.

12. Type of article indicated as needed

Enzensberger W, Fischer PA. Metronome in Parkinson's disease [letter]. Lancet 1996;347:1337. Clement J, De Bock R. Hematological complications of hantavirus nephropathy (HVN) [abstract]. Kidney Int 1992;42:1285.

13. Article containing retraction

Garey CE, Schwarzman AL, Rise ML, Seyfried TN. Ceruloplasmin gene defect associated with epilepsy in EL mice [retraction of Garey CE, Schwarzman AL, Rise ML, Seyfried TN. In: Nat Genet 1994;6:426-31]. Nat Genet 1995;11:104.

14. Article retracted

Liou GI, Wang M, Matragoon S. Precocious IRBP gene expression during mouse development [retracted in Invest Ophthalmol Vis Sci 1994;35:3127]. Invest Ophthalmol Vis Sci 1994;35:1083-8.

15. Article with published erratum

Hamlin JA, Kahn AM. Herniography in symptomatic patients following inguinal hernia repair [published erratum appears in West J Med 1995;162:278]. West J Med 1995;162:28-31.

Books and Other Monographs

(Note: Previous Vancouver style incorrectly had a comma rather than a semicolon between the publisher and the date.)

16. Personal author(s)

Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

17. Editor(s), compiler(s) as author

Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

18. Organization as author and publisher

Institute of Medicine (US). Looking at the future of the Medicaid program. Washington: The Institute; 1992.

19. Chapter in a book

(Note: Previous Vancouver style had a colon rather than a p before pagination.) Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

20. Conference proceedings

Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15-19; Kyoto, Japan. Amsterdam: Elsevier; 1996.

21. Conference paper

Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.

22. Scientific or technical report

Issued by funding/sponsoring agency: Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX): Dept. of Health and Human Services (US), Office of Evaluation and Inspections; 1994 Oct. Report No.: HHSIGOEI69200860. Issued by performing agency: Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work

force and educational issues. Washington: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research.

23. Dissertation

Kaplan SJ. Post-hospital home health care: the elderly's access and utilization [dissertation]. St. Louis (MO): Washington Univ.; 1995.

24. Patent

Larsen CE, Trip R, Johnson CR, inventors; Novoste Corporation, assignee. Methods for procedures related to the electrophysiology of the heart. US patent 5,529,067. 1995 Jun 25.

Other Published Material

25. Newspaper article

Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21;Sect. A:3 (col. 5).

26. Audiovisual material

HIV+/AIDS: the facts and the future [videocassette]. St. Louis (MO): Mosby-Year Book; 1995.

27. Legal material

Public law:
Preventive Health Amendments of 1993, Pub. L. No. 103-183, 107 Stat. 2226 (Dec. 14, 1993).
Unenacted bill:
Medical Records Confidentiality Act of 1995, S. 1360, 104th Cong., 1st Sess. (1995).

Code of Federal Regulations:
Informed Consent, 42 C.F.R. Sect. 441.257 (1995).
Hearing:
Increased Drug Abuse: the Impact on the Nation's Emergency Rooms: Hearings Before the Subcomm. on Human Resources and Intergovernmental Relations of the House Comm. on Government Operations, 103rd Cong., 1st Sess. (May 26, 1993).

28. Map

North Carolina. Tuberculosis rates per 100,000 population, 1990 [demographic map]. Raleigh: North Carolina Dept. of Environment, Health, and Natural Resources, Div. of Epidemiology; 1991.

29. Book of the Bible

The Holy Bible. King James version. Grand Rapids (MI): Zondervan Publishing House; 1995. Ruth 3:1-18.

30. Dictionary and similar references

Stedman's medical dictionary. 26th ed. Baltimore: Williams & Wilkins; 1995. Apraxia; p. 119-20.

31. Classical material

The Winter's Tale: act 5, scene 1, lines 13-16. The complete works of William Shakespeare. London: Rex; 1973.

Unpublished Material

32. In press

(Note: NLM prefers "forthcoming" because not all items will be printed.) Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med. In press 1996.

Electronic Material

33. Journal article in electronic format

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis [serial online] 1995 Jan-Mar [cited 1996 Jun 5];1(1):[24 screens]. Available from: URL: http://www.cdc.gov/ncidod/EID/eid.htm

34. Monograph in electronic format

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reeves JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego: CMEA; 1995.

35. Computer file

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

Tables:

Type or print out each table with double spacing on a separate sheet of paper. Do not submit tables as photographs. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in

the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes use the following symbols, in this sequence:

Identify statistical measures of variations, such as standard deviation and standard error of the mean.

Do not use internal horizontal and vertical rules.

Be sure that each table is cited in the text.

If you use data from another published or unpublished source, obtain permission and acknowledge them fully.

The use of too many tables in relation to the length of the text may produce difficulties in the layout of pages. Examine issues of the journal to which you plan to submit your paper to estimate how many tables can be used per 1000 words of text.

The editor, on accepting a paper, may recommend that additional tables containing important backup data too extensive to publish be deposited with an archival service, such as the National Auxiliary Publication Service in the United States, or made available by the authors. In that event an appropriate statement will be added to the text. Submit such tables for consideration with the paper.

Illustrations (Figures):

Submit the required number of complete sets of figures. Figures should be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Instead of original drawings, x-ray films, and other material, send sharp, glossy, black-and-white photographic prints, usually 127 × 173 mm (5 × 7 inches) but no larger than 203 × 254 mm (8 × 10 inches). Letters, numbers, and symbols should be clear and even throughout and of sufficient size that when reduced for publication each item will still be legible. Titles and detailed explanations belong in the legends for illustrations not on the illustrations themselves.

Each figure should have a label pasted on its back indicating the number of the figure, author's name, and top of the figure. Do not write on the back of figures or scratch or mar them by using paper clips. Do not bend figures or mount them on cardboard.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background.

If photographs of people are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph (see Protection of Patients' Rights to Privacy).

Figures should be numbered consecutively according to the order in which they have been first cited in the text. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required irrespective of authorship or publisher except for documents in the public domain.

For illustrations in color, ascertain whether the journal requires color negatives, positive transparencies, or color prints. Accompanying drawings marked to indicate the region to be reproduced may be useful to the editor. Some journals publish illustrations in color only if the author pays for the extra cost.

Legends for Illustrations:

Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

Units of Measurement:

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be given in degrees Celsius. Blood pressures should be given in millimeters of mercury.

All hematologic and clinical chemistry measurements should be reported in the metric system in terms of the International System of Units (SI). Editors may request that alternative or non-SI units be added by the authors before publication.

Abbreviations and Symbols:

Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

Sending the Manuscript to the Journal:

Send the required number of copies of the manuscript in a heavy-paper envelope, enclosing the copies and figures in cardboard, if necessary, to prevent the photographs from being bent. Place photographs and transparencies in a separate heavy-paper envelope.

Manuscripts must be accompanied by a covering letter signed by all coauthors. This must include 1) information on prior or duplicate publication or submission elsewhere of any part of the work as defined earlier in this document; 2) a statement of financial or other relationships that might lead to a conflict of interest (see below); 3) a statement that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work; and 4) the name, address, and telephone number of the corresponding author, who is responsible for communicating with the other authors about revisions and final approval of the proofs. The letter should give any additional information that may be helpful to the editor, such as the type of article in the particular journal that the manuscript represents and whether the author(s) would be willing to meet the cost of reproducing color illustrations.

The manuscript must be accompanied by copies of any permissions to reproduce published material, to use illustrations or report information about identifiable people, or to name people for their contributions.

Separate Statements:

Definition of a Peer-Reviewed Journal:

A peer-reviewed journal is one that has submitted most of its published articles for review by experts who are not part of the editorial staff. The number and kind of manuscripts sent for review, the number of reviewers, the reviewing procedures, and the use made of the reviewers' opinions may vary, and therefore each journal should publicly disclose its policies in its instructions to authors for the benefit of readers and potential authors.

Editorial Freedom and Integrity:

Owners and editors of medical journals have a common endeavor-the publication of a reliable and readable journal, produced with due respect for the stated aims of the journal and for costs. The functions of owners and editors, however, are different. Owners have the right to appoint and dismiss editors and to make important business decisions in which editors should be involved to the fullest extent possible. Editors must have full authority for determining the editorial content of the journal. This concept of editorial freedom should be resolutely defended by editors even to the extent of their placing their positions at stake. To secure this freedom in practice, the editor should have direct access to the highest level of ownership, not only to a delegated manager.

Editors of medical journals should have a contract that clearly states the editor's rights and duties in addition to the general terms of the appointment and that defines mechanisms for resolving conflict.

An independent editorial advisory board may be useful in helping the editor establish and maintain editorial policy.

All editors and editors' organizations have the obligation to support the concept of editorial freedom and to draw major transgressions of such freedom to the attention of the international medical community.

Conflict of Interest:

Conflict of interest for a given manuscript exists when a participant in the peer review and publication process-author, reviewer, and editor-has ties to activities that could inappropriately influence his or her judgment, whether or not judgment is in fact affected. Financial relationships with industry (for example, through employment, consultancies, stock ownership, honoraria, expert testimony), either directly or through immediate family, are usually considered to be the most important conflicts of interest. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion.

Public t rust in the peer review process and the credibility of published articles depend in part on how well conflict of interest is handled during writing, peer review, and editorial decision making. Bias can often be identified and eliminated by careful attention to the scientific methods and conclusions of the work. Financial relationships and their effects are less easily detected than other conflicts of interest. Participants in peer review and publication should disclose their conflicting interests, and the information should be made available so that others can judge their effects for themselves. Because readers may be less able to

detect bias in review articles and editorials than in reports of original research, some journals do not accept reviews and editorials from authors with a conflict of interest.

Authors:

When they submit a manuscript, whether an article or a letter, authors are responsible for recognizing and disclosing financial and other conflicts of interest that might bias the ir work. They should acknowledge in the manuscript all financial support for the work and other financial or personal connections to the work.

Reviewers:

External peer reviewers should disclose to editors any conflicts of interest that could bias their opinions of the manuscript, and they should disqualify themselves from reviewing specific manuscripts if they believe it to be appropriate. The editors must be made aware of reviewers' conflicts of interest to interpret the reviews and judge for themselves whether the reviewer should be disqualified. Reviewers should not use knowledge of the work, before its publication, to further their own interests.

Editors and Staff:

Editors who make final decisions about manuscripts should have no personal financial involvement in any of the issues they might judge. Other members of the editorial staff, if they participate in editorial decisions, should provide editors with a current description of their financial interests (as they might relate to editorial judgments) and disqualify themselves from any decisions where they have a conflict of interest. Published articles and letters should include a description of all financial support and any conflict of interest that, in the editors' judgment, readers should know about. Editorial staff should not use the information gained through working with manuscripts for private gain.

Project-Specific Industry Support for Research:

Authors:

Scientists have an ethical obligation to submit creditable research results for publication. Moreover, as the persons directly responsible for their work, scientists should not enter into agreements that interfere with their control over the decision to publish the papers they write.

Editors and Staff:

Editors who make final decisions about manuscripts should have no personal financial involvement in any of the issues they might judge. Other members of the editorial staff, if they participate in editorial decisions, should provide editors with a current description of their financial interests (as they might relate to editorial judgments) and disqualify themselves from any decisions where they have a conflict of interest. Published articles and letters should include a description of all financial support and any conflict of interest that, in the editors' judgment, readers should know about. Editorial staff should not use the information gained through working with manuscripts for private gain.

Editors should require authors to describe the role of outside sources of project support, if any, in study design; in the collection, analysis and interpretation of data; and in the writing of the report. If the supporting

source had no such involvement, the authors should so state. Because the biases potentially introduced by the direct involvement of supporting agencies in research are analogous to methodological biases of other sorts (e.g., study design, statistical and psychological factors), the type and degree of involvement of the supporting agency should be described in the Methods section. Editors should also require disclosure of whether or not the supporting agency controlled or influenced the decision to submit the final manuscript for publication.

Corrections, Retractions, and "Expressions of Concern" about Research Findings:

Editors must assume initially that authors are reporting work based on honest observations. Nevertheless, two types of difficulty may arise.

First, errors may be noted in published articles that require the publication of a correction or erratum of part of the work. It is conceivable that an error could be so serious as to vitiate the entire body of the work, but this is unlikely and should be handled by editors and authors on an individual basis. Such an error should not be confused with inadequacies exposed by the emergence of new scientific information in the normal course of research. The latter require no corrections or withdrawals.

The second type of difficulty is scientific fraud. If substantial doubts arise about the honesty of work, either submitted or published, it is the editor's responsibility to ensure that the question is appropriately pursued (including possible consultation with the authors). However, it is not the task of editors to conduct a full investigation or to make a determination; that responsibility lies with the institution where the work was done or with the funding agency. The editor should be promptly informed of the final decision, and if a fraudulent paper has been published, the journal must print a retraction. If this method of investigation does not result in a satisfactory conclusion, the editor may choose to publish an expression of concern with an explanation.

The retraction or expression of concern, so labeled, should appear on a numbered page in a prominent section of the journal, be listed in the contents page, and include in its heading the title of the original article. It should not simply be a letter to the editor. Ideally, the first author should be the same in the retraction as in the article, although under certain circumstances the editor may accept retractions by other responsible people. The text of the retraction should explain why the article is being retracted and include a bibliographic reference to it.

The validity of previous work by the author of a fraudulent paper cannot be assumed. Editors may ask the author's institution to assure them of the validity of earlier work published in their journals or to retract it. If this is not done they may choose to publish an announcement to the effect that the validity of previously published work is not assured.

Confidentiality:

Manuscripts should be reviewed with due respect for authors' confidentiality. In submitting their manuscripts for review, authors entrust editors with the results of their scientific work and creative effort, on which their reputation and career may depend. Authors' rights may be violated by disclosure of the confidential details of the review of their manuscript. Reviewers also have rights to confidentiality, which must be respected by the editor. Confidentiality may have to be breached if dishonesty or fraud is alleged but otherwise must be honored.

Editors should not disclose information about manuscripts (including their receipt, their content, their status in the reviewing process, their criticism by reviewers, or their ultimate fate) to anyone other than the authors themselves and reviewers.

Editors should make clear to their reviewers that manuscripts sent for review are privileged communications and are the private property of the authors. Therefore, reviewers and members of the editorial staff should respect the authors' rights by not publicly discussing the authors' work or appropriating their ideas before the manuscript is published. Reviewer s should not be allowed to make copies of the manuscript for their files and should be prohibited from sharing it with others, except with the permission of the editor. Editors should not keep copies of rejected manuscripts.

Opinions differ on whether reviewers should remain anonymous. Some editors require their reviewers to sign the comments returned to authors, but most either request that reviewers' comments not be signed or leave the choice to the reviewer. When comments are not signed the reviewers' identity must not be revealed to the author or anyone else.

Some journals publish reviewers' comments with the manuscript. No such procedure should be adopted without the consent of the authors and reviewers. However, reviewers' comments may be sent to other reviewers of the same manuscript, and reviewers may be notified of the editor's decision.

Medical Journals and the Popular Media:

The public's interest in news of medical research has led the popular media to compete vigorously to get information about research as soon as possible. Researchers and institutions sometimes encourage the reporting of research in the popular media before full publication in a scientific journal by holding a press conference or giving interviews.

The public is entitled to important medical information without unreasonable delay, and editors have a responsibility to play their part in this process. Doctors, however, need to have reports available in full detail before they can advise their patients about the reports' conclusions. In addition, media reports of scientific research before the work has been peer reviewed and fully published may lead to the dissemination of inaccurate or premature conclusions.

Editors may find the following recommendations useful as they seek to establish policies on these issues.

1. Editors can foster the orderly transmission of medical information from researchers, through peer-reviewed journals, to the public. This can be accomplished by an agreement with authors that they will not publicize their work while their manuscript is under consideration or awaiting publication and an agreement with the media that they will not release stories before publication in the journal, in return for which the journal will cooperate with them in preparing accurate stories (see below).
2. Very little medical research has such clear and urgently important clinical implications for the public's health that the news must be released before full publication in a journal. In such exceptional circumstances, however, appropriate authorities responsible for public health should make the decision and should be responsible for the advance dissemination of information to physicians and the media. If the author and the appropriate authorities wish to have a manuscript

considered by a particular journal, the editor should be consulted before any public release. If editors accept the need for immediate release, they should waive their policies limiting prepublication publicity.

3. Policies designed to limit prepublication publicity should not apply to accounts in the media of presentations at scientific meetings or to the abstracts from these meetings (see Redundant or Duplicate Publication). Researchers who present their work at a scientific meeting should feel free to discuss their presentations with reporters, but they should be discouraged from offering more detail about their study than was presented in their talk.
4. When an article is soon to be published, editors may wish to help the media prepare accurate reports by providing news releases, answering questions, supplying advance copies of the journal, or referring reporters to the appropriate experts. This assistance should be contingent on the media's cooperation in timing their release of stories to coincide with the publication of the article.

Policies for Posting Biomedical Journal Information on the Internet:

Electronic publishing (which includes the Internet) is publishing. Authors, editors, and publishers of biomedical journals who post medical and health information connected to these publications on the Internet should follow the policies established by the International Committee of Medical Journal Editors as the "Uniform Requirements for Authors Submitting Articles to Biomedical Journals" and related statements.

The nature of the Internet requires some special considerations within these well established and accepted policies. As a minimum, sites should indicate the names of editors, authors, and contributors and their affiliations, relevant credentials, and relevant conflicts of interest; documentation and attribution of references and sources for all content; information about copyright; disclosure of site ownership; and disclosure of sponsorship, advertising, and commercial funding.

Linking from one health or medical Internet site to another may be perceived as a recommendation of the quality of the second site. Journals thus should exercise caution in linking to other sites. If links to other sites are posted as a result of financial considerations, such should be clearly indicated. All dates of content posting and updating should be indicated. In electronic, as in print layout, advertising and promotional messages should not be juxtaposed with editorial content. Any commercial content should be clearly identified as such.

Advertising:

Most medical journals carry advertising, which generates income for their publishers, but advertising must not be allowed to influence editorial decisions. Editors must have full responsibility for advertising policy. Readers should be able to distinguish readily between advertising and editorial material. The juxtaposition of editorial and advertising material on the same products or subjects should be avoided, and advertising should not be sold on the condition that it will appear in the same issue as a particular article.

Journals should not be dominated by advertising, but editors should be careful about publishing advertisements from only one or two advertisers as readers may perceive that the editor has been influenced by these advertisers.

Journals should not carry advertisements for products that have proved to be seriously harmful to health-for example, tobacco. Editors should ensure that existing standards for advertisements are enforced or develop their own standards. Finally, editors should consider all criticisms of advertisements for publication.

Supplements:

Supplements are collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as a second part of a regular issue, and are usually funded by sources other than the journal's publisher. Supplements can serve useful purposes: education, exchange of research information, ease of access to focused content, and improved cooperation between academic and corporate entities. Because of the funding sources, the content of supplements can reflect biases in choice of topics and viewpoints.

Editors should therefore consider the following principles.

1. The journal editor must take full responsibility for the policies, practices, and content of supplements. The journal editor must approve the appointment of any editor of the supplement and retain the authority to reject papers.
2. The sources of funding for the research, meeting, and publication should be clearly stated and prominently located in the supplement, preferably on each page. Whenever possible, funding should come from more than one sponsor.
3. Advertising in supplements should follow the same policies as those of the rest of the journal.
4. Editors should enable readers to distinguish readily between ordinary editorial pages and supplement pages.
5. Editing by the funding organization should not be permitted.
6. Journal editors and supplement editors should not accept personal favors or excessive compensation from sponsors of supplements.
7. Secondary publication in supplements should be clearly identified by the citation of the original paper. Redundant publication should be avoided.

The Role of the Correspondence Column:

All biomedical journals should have a section carrying comments, questions, or criticisms about articles they have published and where the original authors can respond. Usually, but not necessarily, this may take the form of a correspondence column. The lack of such a section denies readers the possibility of responding to articles in the same journal that published the original work.

Competing Manuscripts Based on the Same Study:

Editors may receive manuscripts from different authors offering competing interpretations of the same study. They have to decide whether to review competing manuscripts submitted to them more or less simultaneously by different groups or authors, or they may be asked to consider one such manuscript while a competing manuscript has been or will be submitted to another journal. Setting aside the unresolved

question of ownership of data, we discuss here what editors ought to do when confronted with the submission of competing manuscripts based on the same study.

Two kinds of multiple submissions are considered: submissions by coworkers who disagree on the analysis and interpretation of their study, and submissions by coworkers who disagree on what the facts are and which data should be reported.

The following general observations may help editors and others dealing with this problem.

Differences in Analysis or Interpretation:

Journals would not normally wish to publish separate articles by contending members of a research team who have differing analyses and interpretations of the data, and submission of such manuscripts should be discouraged. If coworkers cannot resolve their differences in interpretation before submitting a manuscript, they should consider submitting one manuscript containing multiple interpretations and calling their dispute to the attention of the editor so that reviewers can focus on the problem. One of the important functions of peer review is to evaluate the authors' analysis and interpretation and to suggest appropriate changes to the conclusions before publication. Alternatively, after the disputed version is published, editors may wish to consider a letter to the editor or a second manuscript from the dissenting authors. Multiple submissions present editors with a dilemma. Publication of contending manuscripts to air authors' disputes may waste journal space and confuse readers. On the other hand, if editors knowingly publish a manuscript written by only some of the collaborating team, they could be denying the rest of the team their legitimate coauthorship rights.

Differences in Reported Methods or Results:

Workers sometimes differ in their opinions about what was actually done or observed and which data ought to be reported. Peer review cannot be expected to resolve this problem. Editors should decline further consideration of such multiple submissions until the problem is settled. Furthermore, if there are allegations of dishonesty or fraud, editors should inform the appropriate authorities.

The cases described above should be distinguished from instances in which independent, non-collaborating authors submit separate manuscripts based on different analyses of data that are publicly available. In this circumstance, editorial consideration of multiple submissions may be justified, and there may even be a good reason for publishing more than one manuscript because different analytical approaches may be complementary and equally valid.

About the ICMJE:

The International Committee of Medical Journal Editors (ICMJE) is an informal group whose participants fund their work on the URM. The ICMJE is not a membership organization. Editors are encouraged to join organizations that offer educational programs, meetings, publications, and other opportunities to interact with colleagues.

Examples of such groups are given below.

Council of Science Editors (CSE)
http://www.councilscienceeditors.org/
The European Association of Science Editors (EASE)
http://www.ease.org.uk/
Society for Scholarly Publishing (SSP) http://www.sspnet.org/
The World Association of Medical Editors (WAME)
http://www.wame.org/

Authors of the Current Uniform Requirements and Separate Statements:

The ICMJE participating journals and organizations and their representatives who approved the revised Uniform Requirements in May 2000 should be cited as authors of the documents on this website.

Frank Davidoff, Annals of Internal Medicine; Fiona Godlee, BMJ; John Hoey, Canadian Medical Association Journal; Richard Glass, JAMA; John Overbeke, Nederlands Tijdschrift voor Geneeskunde; Robert Utiger, New England Journal of Medicine; M.Gary Nicholls, New Zealand Medical Journal; Richard Horton, The Lancet; Magne Nylenna, Tidsskrift for Den Norske legeforening; Liselotte Hojgaard, Ugeskrift for Laeger. Sheldon Kotzin, U.S. National Library of Medicine.

Acknowledgments:

The following members of the ICMJE helped author the 1997 version and should be acknowledged in citations of the May 2000 version.

Linda Hawes Clever, Western Journal of Medicine; Lois Ann Colaianni, U.S. National Library of Medicine; George Lundberg, JAMA; Richard G. Robinson, New Zealand Medical Journal; Richard Smith, BMJ; Bruce P. Squires, Canadian Medical Association Journal; Martin VanDer Weyden, The Medical Journal of Australia; and Patricia Woolf, Princeton University.

Inquiries about the Uniform Requirements only should be sent to Christine Laine, MD, MPH at the ICMJE secretariat office, American College of Physicians-American Society of Internal Medicine, 190 N. Independence Mall West, Philadelphia, PA 19106-1572, USA. Phone, 215-351-2660; fax, 215-351-2644; e-mail: claine@mail.acponline.org. Please do not send inquiries about individual journal styles and policies to this address.

The Uniform Requirements has been published in several journals. Please cite a version that appeared in the primary journal literature on or after 1 January 1997; for example:

International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals. Ann Intern Med. 1997;126:36-47.

Uniform Requirements for Manuscripts | URM Journals List | About the ICMJE

International Committee of Medical Journal Editors http://www.icmje.org/

ASSESS-AKI Manuscript Proposal Format

(1) Summary Information
   (a) Full Proposal Title
   (b) Abbreviated Title (Up to 50 letters and spaces)
   (c) Proposed Writing Committee (Including sponsor if first author is not a *ASSESS-AKI Investigator*)
   (d) Abstract/Brief Description (Events, Longitudinal, Cross-sectional, Methods)
   (e) Type of Manuscript (Main, Ancillary Study, Title & PI for Ancillary)
   (f) Data Analysis locations (DCC or Local) and timing (interim data needed?)
   (g) Additional Comments

(2) Proposal Details
   (a) Introduction (Brief rationale and background)
   (b) Research Hypothesis (Clear statement of scientific questions to be addressed)
   (c) Data (List of variables to be used, biological samples including volume of samples if relevant)
   (d) Analysis plan and methods in consultation with the DCC (Detailed description of proposed statistical analyses)
   (e) Relationship of the proposed manuscript to other ASSESS-AKI abstracts, manuscripts, approved/pending manuscript proposals, and specific aims of approved ancillary studies.
   (f) Proposed mock-up tables and figures (if possible)
   (g) Proposed journal(s) for submission

References (if available)

15 CLINICAL RESEARCH CENTER PHASE-OUT

This General Manual of Procedures (MOP) section details ASSESS-AKI clinical research center (CRC) phase-out procedures.

Before ASSESS-AKI CRC participation may be phased out, the following criteria must be met for closeout of each protocol in which a given CRC has participated:

- Last subject/last visit complete
- All CRC queries addressed
- All sample and genetic data is accounted for the in the BST

15.A Phase-Out IRB Requirements

After the primary manuscript has been published, CRCs may allow IRB approvals to remain open for analysis only.

As CRCs phase out of ASSESS-AKI participation, each CRC must identify an individual to be responsible for closing out all ASSESS-AKI protocol IRB approvals upon conclusion of any post-primary manuscript analysis.

15.B ASSESS-AKI CRC Phase-out Checklist

The ASSESS-AKI CRC Phase-Out Checklist (Appendix 15.D) must be completed by the CRC study team to assure that all items required for network involvement closeout are considered, completed, and (where specified) sent to the DCC. Of particular importance is the checklist section regarding future study record storage. Additionally, items specified with an asterisk (*) on the checklist must be sent to the DCC at ASSESS_AKI_Compliance for review and storage.

When complete with PI signature, the ASSESS-AKI CRC Phase-Out Checklist Part A is sent to the DCC at ASSESS_AKI_Compliance for review, reconciliation, and approval. The University of Washington is the last ASSESS CRC to phase out.

After April 30, 2018, Part B can be completed. When complete with PI signature, the ASSESS-AKI CRC Phase-Out Checklist Part B is sent to the DCC at ASSESS_AKI_Compliance for review, reconciliation, and approval.

Upon DCC approval of both Part A and Part B of the ASSESS-AKI CRC Phase-out Checklist, the CRC's ASSESS-AKI participation is complete.

15.C Study Records Retention Policy

Study records must be maintained at the CRC in accordance with Good Clinical Practice:

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf. Additionally, applicable regulatory guidelines and institutionally specific policies must be followed, whichever are the most stringent. The CRC will identify long-term storage information (date sent, location,

contact) for the protocol documents and maintain retrieval instructions. Information regarding applicable federal guidelines and details for electronic data storage may be found in ASSESS-AKI General MOP section 15: Study Records Retention Policy.

If local storage limitations require original paper-format source documents to be converted to electronic format (i.e. compact disc or PDF) before the relevant federal regulatory retention periods above have expired, the CRC should send its Standard Operating Procedure (SOP) for creating certified electronic copies to theDCC Principal Investigator. ASSESS_AKI_Compliance.

15.D ASSESS-AKI CRC Phase-out Checklist Part A

ASSESS-AKI CRC Phase-out Checklist Part A

Principal Investigator _____ CRC # _____

ASSESS-AKI protocols for which CRC enrolled participants:

(Check all that apply)

☐ Protocol 1- Adults
☐ Protocol 2 - Pediatric

In order to execute phase-out of ASSESS-AKI involvement, consider/complete all actions below for all applicable ASSESS-AKI protocols.

PART A

Participant Records
☐ Review and ensure all essential/regulatory documents are current, complete, accurate, and filed appropriately
☐ Review and ensure all research records are complete, accurate, and filed appropriately
☐ Ensure notes-to-file exist for any violations/exceptions that require additional explanation

Unobligated Participant Biospecimen(s)
☐ Notify the DCC if unobligated samples are available
☐ When cleared by the DCC, store or discard according to institutional policy

Document Collation and Storage
Email pdf of items marked * below to ASSESS_AKI_Compliance
☐ IRB termination letter or IRB documentation indicating study is open for analysis only*
☐ Create and file written inventory of all items to be stored
☐ ASSESS-AKI Registry log and Registry form binder
☐ Case and Control Participant Assignment Logs linking participant names and ID numbers (which also serves as the completed participant identification code list required by ICH GCP guidelines)
☐ All study documents bearing participant names
☐ All study documents bearing participant ID numbers
☐ Duality of interest documents
☐ Final report by investigator to IRB

As detailed in ASSESS-AKI General Manual of Procedures (MOP) section 15, study records are considered medical records and should be stored under the applicable

guidelines of federal, state and local regulations. ASSESS-AKI CRCs should consult their institutional records retention policy. Taking into account NIDDK, HIPAA and site-specific records retention requirements applicable for a given study, the policy with the longest period of required record retention should be followed.

Should local storage limitations require original paper-format source documents to be converted to electronic format (i.e. compact disc or PDF) before the relevant federal regulatory retention periods above have expired, the CRC must first send its Standard Operating Procedure (SOP) for creating certified electronic copies to the DCC Principal Investigator for review and approval. Please consult ASSESS-AKI General MOP section 15 for additional details.

Indicate long-term storage information for each applicable ASSESS-AKI protocol:

Protocol	**Date records sent to long-term storage**	**Long-term storage location with contact information**
P1 Adults		
P2 Pediatric		

Cryovial Labels/ TRAILS B

Only the ASSESS-AKI items listed below must be addressed; all other ASSESS-AKI hardware and consumables are considered to be property of the CRC.

Upon resolution of ALL ASSESS-AKI queries and DCC confirmation that all samples have been received by the NIDDK Biorepository and/or ASSESS-AKI Central Lab, the following may be processed for phase-out.

☐ Cryovial labels sent to DCC

☐ TRAILS B questionnaires sent to the DCC (Adult CRCs only)

Website and Data Management Application Access:

☐ Review the attached table of user access at your CRC

- ☐ Identify at least one individual that will maintain access to the data management application for query resolution and, if applicable, sample shipment(s) in Comments field below (include name, phone number and email address)
- ☐ The lead coordinator should complete a close out request for any individuals that no longer need access to the website or database management application. The close out form is located on the homepage of the ASSESS-AKI secure website
  Do not complete a close out request for site investigators or the one individual identified for query resolution.

Comments _____

Signature indicating Part A has been considered and/or completed as directed, and documentation with asterisk (*) above have been emailed to the DCC at ASSESS_AKI_Compliance

_____ _____
Principal Investigator Signature Date

Institutional Research Affairs Contact:

_____ _____ _____
Name Email Address Telephone Number

Email a pdf of this completed and signed Part A form to ASSESS_AKI_Compliance

For DCC Use Only:

- ☐ All required items for Part A submitted to the DCC

_____ _____
DCC Personnel Signature Date

15.E

15. E ASSESS-AKI CRC Phase-out Checklist Part B

ASSESS-AKI CRC Phase-out Checklist Part B

Principal Investigator _____ CRC # _____

ASSESS-AKI protocols for which CRC enrolled participants:

(Check all that apply)

☐ Protocol 1- Adults
☐ Protocol 2 - Pediatric

In order to execute phase-out of ASSESS-AKI involvement, consider/complete all actions below for all applicable ASSESS-AKI protocols.

PART B

Participant Records

☐ Submit last invoice for FedEx shipping marked "FINAL"*

Website and Data Management Application Access:

☐ After April 30, 2018, the individual identified for query resolution should complete a close out request for any investigators and himself/herself that no longer need access to the website or database management application. The close out form is located on the homepage of the ASSESS secure website.

Comments _____

Signature indicating Part B has been considered and completed as directed, and documentation with asterisk (*) above have been emailed to the DCC at ASSESS_AKI_Compliance

_____ _____
Principal Investigator Signature Date

Email a pdf of this completed and signed Part B form to ASSESS_AKI_Compliance

For DCC Use Only:

☐ All required items of Part B submitted to the DCC

_____ _____
DCC Personnel Signature Date

ASsessment,
Serial Evaluation, and
Subsequent Sequelae in AKI
NIH/NIDDK

Protocol Manual of Procedures (MOP)

Version:

April 2020

1 PROTOCOL- SPECIFIC PROCEDURES

1.1 ACUTE KIDNEY INJURY (AKI)

Acute kidney injury (AKI) refers to a sudden, unexpected decrease in kidney function. This phenomenon has been best studied among hospitalized patients. It is well known that dialysis-requiring AKI is associated with a high risk (>30%) of short-term mortality.[1, 2] The importance of AKI as a clinical and public health problem is underscored by recent studies showing a rising incidence in the U.S. over the past several decades.[2, 3]

The vast majority of published studies on AKI have focused only on clinical outcomes that occur during the index hospitalization complicated by AKI and have been limited by several methodological challenges. Thus, relatively little is known about long-term clinical outcomes among patients who suffer hospital-acquired AKI, including the risk of development and acceleration of chronic kidney disease (CKD), death, cardiovascular events, and other important patient-centered outcomes. The 2005 American Society of Nephrology Renal Research Report listed as a research priority "increased epidemiologic research in acute kidney injury." The report also listed as one of the "critically important gaps in knowledge" in the field of AKI that "there are no data on long-term outcomes" after an episode of AKI.[1]

1. American Society of Nephrology Renal Research Report. J Am Soc Nephrol 2005;16:1886-903.
2. Shusterman N, Strom BL, Murray TG, Morrison G, West SL, Maislin G. Risk factors and outcome of hospital-acquired acute renal failure. Clinical epidemiologic study. Am J Med 1987;83:65-71.
3. Liangos O, Wald R, O'Bell JW, Price L, Pereira BJ, Jaber BL. Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. Clin J Am Soc Nephrol 2006;1:43-51.

1.2 ACUTE KIDNEY INJURY (AKI) PARTICIPATION SELECTION (Case)

1.2.1 Definition of Presumed AKI, Adult

For adult (age ≥ 18 years) participants, AKI will be defined as ≥ 50% relative increase OR absolute increase ≥ 0.3 mg/dL (27 umol/L) in peak inpatient serum creatinine compared with baseline outpatient serum creatinine.

For patients with recurrent episodes of AKI during the index hospitalization to be eligible to be enrolled at any episode after the first detected one, they have to meet criteria for non-AKI (ie, minimum of two serum creatinines in between and <=0.2 mg/dL change above baseline) between episodes.

1.2.2 Definition of Presumed AKI, Pediatric

For pediatric (age > 1 month to < 18 years) participants, AKI will be defined as ≥ 50% relative increase in peak inpatient serum creatinine compared with baseline outpatient serum creatinine.

1.2.3 Spectrum of Severity of AKI, Adult

To enhance the likelihood of enrolling an adequate number of adult participants with more severe AKI, we have an enrollment target of at least one third of AKI participants having ≥ 100% relative increase in serum creatinine. To increase the likelihood of having an adequate number of adult participants with AKI due to causes other than rapidly reversible pre-renal azotemia, we have an enrollment target of at least one third of AKI participants who meet AKI criteria lasting ≥ 48 hours. We anticipate that there will be overlap in these two subgroups.

1.3 ALERTS

The Adult/Pediatric (P1/P2_ALERT) forms report a potential serious medical problem or emergency based on clinical observations or reported ASSESS-AKI study information. Blood pressure alerts are based on observations by the Research Coordinator or the PI at the time of the ASSESS-AKI study visit. Acute distress is limited to chest pain, severe respiratory distress, and acute neurological symptoms. ECG alerts are based on clinical observation and/or readings from the test administered to the participant. Specific alerts are based on lab results performed at the Central Lab and the CBC Hemoglobin preformed at the local laboratory. For values on the CBC and/or Dipstick that are outside the reference range, the coordinator should consult with the site PI to see if additional follow-up is needed.

Responses recorded indicate the appropriate disposition of the medical alert whether the information was transmitted to the PI or participant's primary care physician, and if any medical intervention (ER, hospitalization) was initiated. Contact information on the participant's healthcare provider(s) can be found on the CONTACT form and is used to share clinical observations and test results with the participant's health care provider if the participant consents at the start of the study.

If the alerts happen on different days, multiple P1/P2_ALERT forms would be used. For example, there would be multiple alert forms completed related to an elevated BP reading and an out-of-range lab value because the BP value would be recorded on the visit date and the lab value would be recorded on the date that the lab value was received. If more than one alert happens on the same day, those alerts would be recorded on one P1/P2_ALERT form.

P1/P2_ALERT, 1140: For the outpatient annual visits, the value from the Central Lab of the previous ASSESS visit is used to determine a doubling of the serum creatinine. For V3M, Kaiser and Vanderbilt use the outpatient baseline value from V0 to check for serum creatinine doubling at V3M. Montreal uses the local serum creatinine for the V0 vs. V3M comparisons. Yale London Ontario uses the creatinine at discharge for the V0 vs. V3M comparisons.

1.3.1 Pediatric Alert (P2_ALERT)

ECGs would not be useful or have abnormalities in the pediatric participants.

P2_ALERT, Q1010: After December 14, 2012, Stage 2 hypertension is greater than the 99th percentile plus 5mmHg blood pressure for a given height percentile and gender. Prior to December 14, 2102, Stage 2 hypertension is 5mmHg above the 95th percentile blood pressure for a given height percentile and gender.

The RC will need to have the blood pressure norms chart for children as well as a growth curve. Plot the child on the growth chart and check what the 95th percentile blood pressure is.

For Pediatric participants greater than 18 years of age, use the systolic blood pressure is > 140 mmHg; diastolic blood pressure is > 90 mmHg.

1.4 APPOINTMENTS: CONFIRMING AND SCHEDULING

Explain the importance of completing the visits within the visit windows and verify that the participant will be able to make all of the scheduled visits and phone contacts. The study participant (if applicable, parent/guardian) should consider work, school, and sports schedules, along with upcoming vacations when finalizing a schedule.

Include a copy of the ASSESS-AKI Participant Visit Schedule(s) in the participant's study handout folder so that he/she can adjust his/her schedules for the best adherence. Include a copy of this schedule in the participant's study folder at the Clinical Research Center (CRC).

At each visit/phone contact, document the date the study contact actually occurred and review the ASSESS-AKI Visit Scheduler Report to confirm the date of the next scheduled appointment. The Research Coordinator should update the site's appointment book or calendar with the next study contact.

If a participant routinely fails to keep scheduled visits, the study participant (if applicable, parent/guardian) should be counseled by the Research Coordinator and, possibly, by the Principal Investigator (PI) at the CRC. If such counseling does not improve the participant's adherence, contact the Data Coordinating Center (DCC) for guidance.

The last participant visit for Yale University Sites (Montreal, Cincinnati, New Haven, and London Ontario), Vanderbilt University, and Kaiser Permanente of Northern California was on or before November 30, 2017. The University of Washington will continue conducting appointments.

1.4.1 Visit Scheduler

The Visit Scheduler provides a list of ideal visit dates along with the acceptable range for each study contact. The Research Coordinator is encouraged to run the visit schedule upon completion of the Inpatient Checklist 2 (P1/P2_INPATIENT2) form to determine the ideal Visit 3M date and window. For an AKI participant, Time Zero is the date of the AKI episode. For a Non-AKI participant, Time Zero is the date of discharge. See TIME ZERO in the PROTOCOL SPECIFIC MOP for additional information.

The schedule must be produced again at the Visit 3M to forecast the rest of the study contacts. The table below describes the ASSESS-AKI visit windows. The ideal visit date is listed as the number of days from a particular visit, along with the window.

- Visits should be scheduled on the ideal visit date whenever possible. When the visit cannot be scheduled on the ideal visit date, schedule the visit within the visit window. The visit window is ±four weeks for the Visit 3M and ±six weeks for the outpatient contacts. If a situation arises where Visit 3M cannot take place within the visit window, please contact the scientific coordinator at the DCC to request an exception prior to performing the interview or biomarker collection. Visits that occur before or after the visit window, except with Visit 3M, and any skipped visits need to be documented by the CRC. A spreadsheet is posted on the ASSESS website for each CRC to document these occurrences. The Visit Exceptions spreadsheets can be found on the ASSESS website, and the coordinator has access only to its site's spreadsheet. Refer to the Document Management MOP, Section 2 for more information on how to fill out the spreadsheet. There are also instructions in the

Visit Window Exceptions folder under "How to Document Protocol Exceptions" and "How to Edit and Repost Visit Window Spreadsheet." The website does not support new documents with an "x" on the end of the extension. For example, only documents that are .doc or .xls are supported, not documents that are .docx or .xlsx.

Visit Number	Ideal Date (Days from Visit 0)	Visit Window
0	TIME ZERO	-
3M	91 days (63-119 days)	+/- 28 days (4 weeks)
Visit Number	**Ideal Date (Weeks from Visit 3M)**	**Visit Window**
3M	0	
6M (phone contact)	91 days (49 – 133 days)	+/- 42 days (6 weeks)
12M	274 days (232 - 316 days)	+/- 42 days (6 weeks)
18M (phone contact)	457 days (415 – 499 days)	+/- 42 days (6 weeks)
24M	639 days (597 – 681 days)	+/- 42 days (6 weeks)
30M (phone contact)	822 days (780 – 864 days)	+/- 42 days (6 weeks)
36M	1005 days (963 – 1047 days)	+/- 42 days (6 weeks)
42M (phone contact)	1187 days (1145 – 1229 days)	+/- 42 days (6 weeks)
48M	1370 days (1328 – 1412 days)	+/- 42 days (6 weeks)
54M (phone contact)	1553 days (1511 – 1595 days)	+/- 42 days (6 weeks)
60M	1736 days (1694 – 1778 days)	+/- 42 days (6 weeks)
66M (phone contact)	1919 days (1877 – 1961 days)	+/- 42 days (6 weeks)
72M	2102 days (2060 – 2144 days)	+/- 42 days (6 weeks)
78M (phone contact)	2285 days (2243 – 2327 days)	+/- 42 days (6 weeks)
84M	2468 days (2426 – 2510 days)	+/- 42 days (6 weeks)
90M (phone contact)	2651 days (2609 – 2693 days)	+/- 42 days (6 weeks)
96M	2,834 days (2,792 - 2,876 days)	+/- 42 days (6 weeks)

1.5 ASSESS-AKI OVERVIEW

ASSESS-AKI will employ a parallel matched prospective cohort of participants with AKI and matched adult participants without AKI to address the proposed Specific Aims. In addition, ASSESS-AKI will use a prospective cohort design and attempt to enroll all eligible children undergoing cardiac surgery as part of the TRIBE-AKI Study. Throughout the remainder of the protocol, we note specifically when there are differences between adult and pediatric ASSESS-AKI participants.

The selected study designs were chosen primarily to answer the primary Specific Aims 1 and 2 in the most efficient manner within the constraints of available resources. ASSESS-AKI will take advantage of existing research efforts involving AKI within participating Clinical Research Centers (CRCs) to identify, recruit, and follow hospitalized participants who do or do not appear to have suffered an episode of AKI based on serum creatinine-based definitions. In its deliberations, the Steering Committee discussed the following principles in considering the final study design and participant selection.

With regard to participants who suffered an inpatient episode of AKI, the Steering Committee identified that the enrolled population should include:

- A wide spectrum of severity of AKI, as currently defined by the magnitude of change in peak inpatient serum creatinine compared with baseline outpatient serum creatinine concentration.
- An acceptable spectrum of type of AKI, broadly characterized as acute tubular necrosis, pre-renal azotemia, and other/unknown.
- A final population distribution that could be achieved across CRCs within a relatively short recruitment period to maximize long-term follow-up.

With regard to participants who did not experience an inpatient episode of AKI, the Steering Committee identified that the enrolled population should:

- Have minimal or no relative and absolute change in peak inpatient serum creatinine compared with baseline outpatient serum creatinine concentration to enhance the likely separation in subsequent event rates during follow-up.
- Be very similar to those with AKI with regard to major baseline confounders based on a prioritized set of criteria used to match individual participants.
- Have a high likelihood of completing long-term follow-up.

1.5.1 Goals

The overall goals of ASSESS-AKI are to make significant contributions to the field of AKI in the five following areas:

- Establishing a diverse prospective parallel, matched cohort of adults and children with and without AKI.
- Characterizing the short-term and long-term natural history of AKI based on current serum creatinine-based diagnostic criteria.
- Evaluating the incremental utility of novel blood and urine biomarkers to refine the diagnosis and prognosis of AKI.

- Developing a prognostic risk score that integrates patient characteristics and biomarkers to help inform providers and patients about the risks of adverse events after an episode of AKI.
- Identifying the subset of high-risk patients with AKI who could be targeted for future interventional clinical trials to improve outcomes after an episode of AKI.

1.5.2 Description

Each clinical research center (CRC) will pursue a minimum of a 1:1 ratio for AKI: Non-AKI participant matching. Vanderbilt will enroll 250 AKI and 250 matched Non-AKI participants into long-term follow-up. The University of Washington will recruit a minimum of 200 AKI and 200 matched Non-AKI participants per CRC enrolled into long-term follow-up. Kaiser will enroll 156 AKI and 156 matched Non-AKI participants into long-term follow-up. Yale will recruit 200 AKI participants and 200 non-AKI participants from the parent TRIBE-AKI study, with a current plan of 300 adults and 100 children. The maximum ratio is 1:3 for AKI:Non-AKI participant matching. More than one AKI participant may not be matched to one non-AKI participant. Once enrolled as either an AKI or a non-AKI participant, the participant may not switch groups. A matching non-AKI participant will be targeted to be enrolled within 12 months after an AKI participant is enrolled into the long-term follow-up (i.e., defined as completion of the three-month study visit). Recruitment of a match is permitted in the opposite manner as well, i.e., a matching AKI participant will be targeted to be enrolled within six months after a non-AKI participant is enrolled into the long-term follow-up, See discussion in *Section D.6.4* of the ASSESS-AKI PROTOCOL for the rationale of the matching approach.

1.6 BASELINE SERUM CREATININE

Only patients with known information on "baseline" serum creatinine and estimated GFR will be included in the ASSESS AKI study.

For each participant at the Kaiser site, Vanderbilt site, and Washington site, the "baseline" serum creatinine concentration will be considered the outpatient, non-emergency department test value nearest to the index hospitalization within 7 and 365 days prior to admission using an IDMS calibrated serum creatinine assay.

If an outside laboratory is using the Siemens/Dade Dimension or NOVA whole blood analyzer, the serum creatinine value may not be used and is not considered to be IDMS calibrated.

Serum creatinines obtained from rehabilitation facilities may be used at the PI's discretion and would need to be documented by the PI in Q6000 of the Baseline Serum Creatinines Measures form (BASE_CREATININE). If it is known that the serum creatinine is seven days prior to any hospitalization, that value should not be used as the baseline serum creatinine, except with elective procedures.

Serum creatinines from prior hospitalizations are not included in the baseline definition.

For each participant at the Yale sites, the "baseline" serum creatinine concentration will be considered the pre-op/outpatient/non-emergency test prior to the index hospitalization within 365 days prior to surgery, excluding newborns of less than one month of age. Please refer to *YALE* for exceptions.

The DCC will verify that the BASE_CREATININE form is reviewed and signed within 15 days after the Eligibility Checklist 2 (ELIG2) visit date for all sites.

1.6.1 Yale

The TRIBE-AKI Study, pre-operative serum creatinine results, from an IDMS calibrated assay obtained within 365 days before cardiac surgery, can be used to define "baseline" kidney function for the subset of participants who are undergoing non-urgent cardiac surgery. One of the participating adult sites (New Haven) currently does not use the IDMS calibrated assay. In addition, for pediatric participants in TRIBE-AKI, we will accept a pre-operative serum creatinine concentration measured in the local hospital clinical laboratory among patients scheduled for elective cardiac surgery. Newborns, which are less than one month old, are not eligible for the study due to falsely elevated baseline creatinine (maternal blood). We note that one of the participating pediatric recruitment sites (Cincinnati) currently use the Jaffe method for measuring serum creatinine.

1.6.2 More Than One Value

If a person has more than one available test result in a calendar day, record the peak value; the results will not be averaged.

1.7 BIOMARKER SAMPLE COLLECTION

1.7.1 Inpatient Biospecimen Collection Plan

Across all adult clinical research centers (CRCs), at least one sample of blood and urine will be obtained (1) for adult AKI participants up to 96 hours after identification of the AKI episode and (2) for adult non-AKI participants any time prior to hospital discharge. The mandatory minimum collection is three 0.5mL aliquots of EDTA plasma and three 1.0mL aliquots of urine for adults. If the minimum is not collected, the adult participant is withdrawn from the study. There is no mandatory minimum collection for pediatric participants during the inpatient phase.

Anuria is defined as <50cc/day and is not a contraindication to urine collection. If there is not enough urine, the coordinator should come back to collect more urine. However, multiple collections should not be pooled; rather the coordinator should come back and collect urine from a longer period of time to meet the minimum urine volume. If an adult AKI participant is unable to produce at least 3cc of urine within the allowable time period due to severity of AKI, then the recruiter will continue to enroll the participant, only collect blood, and request a protocol exception from the DCC Scientific Coordinator.

Inpatient biospecimen samples will be transferred to the NIDDK Biorepository for coordination of future biomarker testing and storage at the NIDDK Biorepository.

For additional details, refer to the BIOSPECIMEN MOP.

1.7.2 Outpatient Biospecimen Collection Plan: Visit 3M

For the outpatient phase, the top priority is sending a single aliquot of serum and a single aliquot of urine from adult participants to the Central Laboratory at all visits. Prior to May 30, 2012, a single aliquot of serum was sent to the local laboratory for serum creatinine measurement at V3M. After May 30, 2012, all aliquots will be sent to the NIDDK Biorepository.

For adults, the mandatory minimum collection at Visit 3M is 10mL of whole blood and 20mL of urine. The Central Lab requires a minimum of 0.35mL of serum for its lab measurements, and 0.05mL is required for the core/Tier 1 biomarker measurements. For pediatric participants, the mandatory minimum at Visit 3M is 1.6mL for diaper wearers and 5mL for non-diaper wearers; there is no mandatory minimum for blood at Visit 3M.

If the participant is unable to provide the minimum volume of blood or urine, there is a 48-hour window of the study visit for collection of the blood and urine samples. Multiple blood and urine samples should not be pooled. If the minimum is not collected within the 48-hour window, reschedule the visit to attempt the collection again within the visit window (+/- four weeks of the ideal date). If the minimum of blood and urine cannot be collected at V3M, the adult participant is withdrawn from the study unless the QCC approves a protocol exception. If the minimum of urine cannot be collected at V3M, the pediatric participant is withdrawn from the study.

For additional details, refer to the BIOSPECIMEN MOP.

1.7.3 Outpatient Biospecimen Collection Plan: Yearly Visits

For adults, there is no mandatory minimum collection for blood or urine at the yearly visits.

For pediatric participants, the mandatory minimum at V12M is 0.175mL of plasma based on 0.150mL to measure serum creatinine and serum Cystatin C and 0.025mL for core/Tier 1 biomarker measurements. Please attempt to collect 0.2mL of plasma in order to send 0.150mL to the Central Lab and 0.05mL to the Biorepository. For diaper-wearers, the mandatory minimum urine volume at V12M is 1.6mL based on requiring 1mL for core/Tier 1 biomarker measurements and 0.275mL for urine albumin and urine creatinine (the latter was doubled if there are measurement issues). For non-diaper-wearers, the mandatory minimum urine volume at V12M is 5mL. After V12M, there is no mandatory minimum collection for blood or urine for pediatric participants.

Specimens may be collected within a 48-hour window of the yearly visit. If the blood and urine samples are not collected within the 48-hour window, the visit may be repeated within the visit window (+/- six weeks of the ideal date). The urine will not be pooled; it may be aliquoted from different time points. If the minimum is collected at one of the time points, that sample will be used and the previous samples discarded.

Outpatient biospecimen samples will be transferred to the Central Lab for core measurements and the NIDDK Biorepository for coordination of future biomarker testing and storage at the NIDDK Biorepository.

For additional details, refer to the BIOSPECIMEN MOP.

1.7.4 Inpatient and Outpatient Biospecimen Collection Plan: Minima and Goals

Visit	Adult					
	Minimum Urine	Goal Urine	Collection Window Urine	Minimum Blood	Goal Blood	Collection Window Blood
0	3 (1mL) aliquots	10 (1mL) aliquots	n/a	EDTA 3 (0.5mL) plasma aliquots	EDTA 6 (0.5mL) aliquots	n/a
3M	20mL	10 (1mL) aliquots	48-hr	10mL whole blood	Serum 6 (1mL) aliquots	48-hr
		3 (10mL) aliquots			EDTA 5 (1mL) aliquots	
		PI 1 (10mL) aliquots			Citrate 2 (1mL) aliquots	
12M	0	10 (1mL) aliquots	48-hr	0	Serum 6 (1mL) aliquots	48-hr
		3 (10mL) aliquots			EDTA 5 (1mL) aliquots	
					Citrate 2 (1mL) aliquots	
24M/ 36M/ 48M/ 60M/ 72M/ 84M	0	10 (1mL) aliquots	48-hr	0	Serum 6 (1mL) aliquots	48-hr
		3 (10mL) aliquots			EDTA 5 (1mL) aliquots	
					Citrate 2 (1mL) aliquots	
		3 (10mL) aliquots			EDTA 5 (1mL) aliquots	
					Citrate 2 (1mL) aliquots	

Vs	Pediatrics						
	Minimum Urine		Goal Urine	Collection Window Urine	Minimum EDTA Plasma	Goal EDTA Plasma	Collection Window Blood
	Diaper	Non-Diaper					
0	0	0	10 (1mL) aliquots		0	4 (0.5mL) aliquots	n/a
3M	1.6mL	5mL	10 (1mL) aliquots	48-hr	0	1 (0.5mL) aliquots	48-hr
			1 (10mL) aliquots			4 (0.25mL) aliquots	
12M	1.6mL	5mL	10 (1mL) aliquots	48-hr	0.175mL	1 (0.5mL) aliquots	48-hr
			1 (10mL) aliquots			4 (0.25mL) aliquots	
24M/ 36M/ 48M/ 60M/ 72M/ 84M	0	0	10 (1mL) aliquots	48-hr	0	1 (0.5mL) aliquots	48-hr
			1 (10mL) aliquots			4 (0.25mL) aliquots	

1.8 BIOMARKER SELECTION

Refer to Section D.13.6 in the *ASSESS-AKI Protocol*.

1.9 BIOSPECIMEN VOLUME COLLECTION PLAN

Refer to the BIOSPECIMEN MOP.

1.10 BLOOD PRESSURE

1.10.1 Blood Pressure

Blood pressure changes and development of hypertension are based on automated blood pressure measurement at study visits by trained research personnel; self-report of a physician diagnosis of hypertension; and/or evidence of a new prescription of an anti-hypertensive agent for the indication of hypertension.

BLOOD_PRESSURE, 1060: A tape measure is used to measure and record the midpoint circumference of the arm used. This measurement is taken on the right arm, which is bare from the shoulder. With the participant standing, holding the forearm horizontal (90 degrees angle), the arm length is measured from the acromion (or boney extremity of the shoulder girdle) to the olecranon (or tip of the elbow) with a metric tape. The midpoint is marked on the dorsal surface of the skin. The participant should relax the arm straight down along the side of the body. The arm circumference is measured by drawing the tape snugly around the arm at the level of the midpoint mark. Keep the tape horizontal, and the tape should not indent the skin.

BLOOD_PRESSURE, 1070: Information on the cuff of the equipment is recorded as a quality control measure.

BLOOD PRESSURE, 1080: Record the first pulse measurement after the participant has remained seated on a chair for five minutes prior to the first seated blood pressure measurement.

BLOOD_PRESSURE, 1150: Add the two lowest systolic measurements and divide by 2.

BLOOD_PRESSURE, 1160: Add the two lowest diastolic measurements and divide by 2.

BLOOD_PRESSURE, 1170-1180: The Research Coordinator will need to have the blood pressure norms chart for children as well as a growth curve. Plot the child on the growth chart and record what the 95th percentile blood pressure is for age, gender, and height. For pediatric participants greater than 17 years of age, Q1170-1180 should be left blank.

After December 14, 2012, Stage 2 hypertension is greater than the 99th percentile plus 5mmHg blood pressure for a given height percentile and gender. Prior to December 14, 2102, Stage 2 hypertension is 5mmHg above the 95th percentile blood pressure for a given height percentile and gender. Refer to ALERTS.

BLOOD_PRESSURE, 1190-1200: The Research Coordinator will need to have the blood pressure norms chart for children as well as a growth curve. Plot the child on the growth chart and record what the participant's percentile blood pressure is for age, gender, and height. For pediatric participants greater than 18 years of age, Q1190-1200 should be left blank.

If the value is elevated, check that you are using the appropriate cuff size and try repositioning the cuff. Elevated values may generate an alert that should be noted on the P1/P2_ALERT form. The mean BP is used to determine if an ALERT form is needed. A participant with elevated blood pressure may be

prescribed anti-hypertensive medications that should be noted on the Concomittant Medications (CMED) form.

If the pediatric participant is very small and the BP cannot read a result, a prior BP may be noted in the comment section of the form but those values should not be used to complete the form.

If the BP is taken manually, place results in the comment section of the form and also state that it is a manual BP reading.

See ALERTS and EQUIPMENTin the PROTOCOL SPECIFIC MOP for more information.

1.10.2 Pediatric Baseline blood Pressures

Baseline blood pressures for all enrolled ASSESS-AKI pediatric participants who have completed V3M will be collected. These values will be recorded on the Baseline Blood Pressure Collection for ASESS spreadsheet that is available by contacting the Yale-New Haven site. If you are unable to find certain data points, please note "NA" on the worksheet. There are four time points that the investigators are interested in reviewing. They include:

1. Pre-Operative
    a. Outpatient: Blood pressures obtained during the last outpatient visit prior to the index hospitalization.
    b. Inpatient: Blood pressures obtained before the start of surgery. Those closest to the time of surgery should be captured.
2. Post-Operative
    a. Outpatient: Blood pressures obtained during the first post-operative outpatient visit.
    b. Inpatient: Blood pressures obtained prior to discharge from the index hospitalization. Those closest to the time of discharge should be captured.

1.11 BLOOD SAMPLING PROCEDURES

If the participant is unable to provide blood, there is a 48-hour window of the study visit for collection of the blood sample of adult and pediatric participants during the outpatient phase. Multiple blood samples should not be pooled. If the blood sample is not collected within the 48-hour window, reschedule the visit to attempt the collection again within the visit window. This window is +/- four weeks of ideal date for Visit 3M and +/-six weeks of ideal date for yearly visits.

See 1.7 BIOMARKER SAMPLE COLLECTION in the PROTOCOL SPECIFIC MOP. Refer to the BIOSPECIMEN MOP.

1.12 CASE SELECTION

See ACUTE KIDNEY INJURY PARTICIPANT SELECTION in the PROTOCOL SPECIFIC MOP.

1.13 CENTRAL LABORATORY

See LABORATORIES in the PROTOCOL SPECIFIC MOP and refer to the BIOSPECIMEN MOP.

1.14 CHRONIC LUNG DISEASE

Examples of chronic lung diseases include chronic obstructive lung disease, reactive airway disease, interstitial lung disease, pulmonary hypertension, cystic fibrosis, chronic lung disease of prematurity, and asthma.

1.15 CONCOMITANT MEDICATIONS

1.15.1 Concomitant Medications

All prescription medications, calcium, Coenzyme Q10, and Vitamin D supplements that the participant takes daily or regularly within the last 30 days preceding a study contact are recorded. Regularly is defined as consistent frequency. If a medication is prescribed for a limited number of days, such as an antibiotic prescribed for 10 to 14 days, it is not recorded.

Refer to the reference, MEDICATION LIST.

1.15.2 Over-the-Counter Concomitant Medications

Aspirin, fish oil supplements, and non-steroidal anti-inflammatory drugs (NSAIDs) taken daily or regularly in the past 30 days are recorded. If the participant took an NSAID for a day to treat a headache or muscle ache, it would not be recorded. Regularly is defined as consistent frequency.

Refer to the reference, CMED_OTC REFERENCE.

1.16 CONFIDENTIALITY

1.16.1 HIPAA (US Sites)

Participants must sign a Health Information Insurance Portability and Accountability Act (HIPAA) Authorization in addition to the informed consent(s). The HIPAA Authorization may or may not be incorporated into the ASSESS-AKI consent depending on the policy of the clinical research center (CRC). If HIPAA language is incorporated into the informed consent form, the regulation mandates that it be submitted to the IRB prior to approval. This form describes the kinds of health information collected for the study, all of the disclosures of health information that will be made, and lists parties to whom the disclosures of personal heath information will be made.

1.16.2 Medical Record Release

This study may require the release of medical records from remote Health Care Facilities. Each CRC must obtain written authorization for the release of medical records from each participant. Check if your institution has a Medical Release Form. London Health Sciences Center uses the Consent for Access or Disclosure of Personal Information and/or Personal Health Information.

1.16.3 Additional Confidentiality Concerns

- Do not record social security numbers without ensuring that the participant answered YES to this specific question on the informed consent.
- Social security numbers will not be data entered.
- Only authorized personnel may be permitted to view these social security numbers.
- Consent forms(s) and HIPAA authorizations must be securely maintained in a separate location from the data collection forms.
- Participants will be assigned a Participant ID number, a unique study identification number.
- The DCC staff has access to the Participant ID number for data management purposes. All communication between the DCC staff and the CRC staff regarding participant data occurs using the Participant ID only.

1.17 CONTACT INFORMATION

The participant's contact information is reviewed and updated at each study contact to facilitate yearly visits and/or telephone contacts. This form contains identifiable participant information (including sociodemographic information such as primary residential address, zip code) and must not be shared with the DCC.

Contact information on the participant's healthcare provider(s) is used to share clinical observations and test results with the participant's health care provider if the participant consents at the start of the study. Healthcare provider includes primary care physician, nephrologist, cardiologist, nurse practitioner, etc.

See TELEPHONE CALLS in the PROTOCOL SPECIFIC MOP and Section 8, PARTICIPANT RETENTION, in the ASSESS-AKI GENERAL MOP for more information.

1.18 CONTRAST GADOLINIUM

Gadolium brands used include, but are not limited to, Magnevist, Eovist, Multihance, and Omniscan.

1.19 CONTROL SELECTION

See NON-AKI PARTICIPANT SELECTION in the PROTOCOL SPECIFIC MOP.

1.20 DATA ENTRY OF V0 FORMS FOR PARTICIPANTS WHO DO NOT PROGRESS TO V3M

For those participants who do not progress to V3M, each site determines if it will data enter all of the V0 forms or if it will data enter the required V0 forms and complete the site-specific Excel spreadsheet, which are explained below.

The following forms are the required V0 forms to be data entered for all participants who do not progress to V3M:

- Eligibility Checklist 1A (ELIG1A)
- Baseline Serum Creatinine Measures (BASE_CREATININE)
- Inpatient Serum Creatinine Measures (INPT_CREATININE)
- Adult/Pediatric Inpatient Specimen Collection (P1_INPT_SPEC/P2_INPT_SPEC)
- Withdrawal (WITHDR)

To complete the site-specific Excel spreadsheet, the coordinator collects and enters the following information on the Excel spreadsheet,

- All matching criteria
- CKD
- CHF
- Diabetes
- Pregnancy
- Creatinine
- Prior CVD
- Dialysis
- Severity of AKI

The Registry data will provide the age, gender, and primary race of the participant. The DCC will periodically request the site-specific Excel spreadsheet.

1.21 DEATH

If a participant signs the informed consent, is enrolled during the inpatient phase, and dies before the three-month visit, the Death Record Evaluation (DEATH_EVAL) and Withdrawal (WITHDR) forms must be completed. Death cannot be data entered as an event until Visit 3M.

If it is discovered at or after V3M that the participant has died AND there is no report by proxy, the Death Record Evaluation (DEATH_EVAL) and Withdrawal (WITHDR) forms must be completed.

If it is discovered at Visit 3M that the participant has died as reported through proxy regardless of location, the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS), the Event Information Sheet (EVENT_INFO), the Death Record Evaluation (DEATH_EVAL), and Withdrawal (WITHDR) forms are completed.

If it is discovered at or after Visit 6M that the participant has died as reported through proxy regardless of the location, the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS), the Event Information Sheet (EVENT_INFO), the Death Record Evaluation (DEATH_EVAL), and Withdrawal (WITHDR) forms are completed.

If death as reported through proxy occurred during a hospitalization/ER visit, the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS), the Event Information Sheet (EVENT_INFO), the Death Record Evaluation (DEATH_EVAL), and the Withdrawal (WITHDR) are completed, and if medical records are available, the Hospital/ER Record Evaluation (HOSP_EVAL), Inpatient Creatinine (INPT_CREATININE), and the ICD9/CPT Adminstrative Codes Sheet/ICD10/CCI Adminstrative Codes Sheet (ICD9_CPT_CODES/ICD10_CCI_CODES) forms should also be completed.

If death as reported through proxy occurred outside of the hospital, the Hospital/ER Record Evaluation (HOSP_EVAL), the Inpatient Creatinine (INPT_CREATININE), and the ICD9/CPT Adminstrative Codes Sheet/ICD10/CCI Adminstrative Codes Sheet (ICD9_CPT_CODES/ICD10_CCI_CODES) forms are not completed.

See EVENTS in the PROTOCOL SPECIFIC MOP and the Event Adjudication Manual of Procedures for more information.

1.22 DEMOGRAPHICS

During Visit 0, date of birth, gender, race, and ethnicity are collected on the REGISTRY form. Participants (and guardians) will be asked about marital status, living arrangements, education, employment, and income at Visit 0 and Visit 3M. Healthcare coverage is asked at every visit. For pediatric participants, these questions are also asked of the guardian(s). A guardian is defined as a mother, father, grandparent, sibling (if 18 years of age or older), aunt/uncle, legal guardian, friend, or other. The number of legal guardians is asked, and the information is collected on one or two legal guardians. If there are no legal guardians, the Research Coordinator should go to the end of the form to complete the question in the shaded box. If there is only one legal guardian, the questions for Guardian 2 should be skipped and the question in the shaded box at the end of the form should be answered by the Research Coordinator.

1.22.1 Marital Status

The participant's current marital status is recorded as never married, currently married, domestic partner, separated, divorced, or widowed. The participant may decide not to answer.

1.22.2 Living Arrangements

The adult participant is asked if he/she lives alone or with others (spouse, children, family members, significant others, roommates). The type of residence includes a home/apartment, nursing home, assisted living facility, or rehabilitation or skilled nursing home facility. The pediatric participant is asked if he/she has lived in the primary residence since birth as well as a description of the residence. A residential center is defined as a group home or nursing facility. If the pediatric participant splits his/her time between two different types of living arrangements, he/she should be asked to identify one as the primary residence. Pediatric participants are asked about the number of siblings, if the siblings live in the same primary residence, and how many parents/guardians live in the household.

1.22.3 Education

The participant is asked the highest level of education that he/she has completed. The participant may decide not to answer. Reference Card A may be used.

1.22.4 Employment

The participant is asked about his/her employment status. Primary employment status is defined as the employment type that represents greater than 50% of the person's professional activities during the past year. If he/she is in school as well as employed full-time, he/she should select his/her desired choice. If the participant is not currently employed, he/she is asked about when the last time was that he/she was employed and the type of work. If the requested month and/or year is unknown of last employed, coordinators will use 98 for month and 9898 for year. Reference Card B and/or C may be used. The Research Coordinator should be available to help a participant select the most appropriate category if the participant is unsure where his/her occupation may fit in the categories provided.

1.22.5 Health Insurance

Current health insurance and type of coverage are asked at every visit. During the inpatient phase, the questions are asked on the Adult/Pediatric Inpatient Demographic Information (P1_INPT_DEMO/P2_INPT_DEMO) form and during the outpatient visits, the questions are on the

Adult/Pediatric Lifestyle V3M (P1_LIFESTYLE_3M/ P2_LIFESTYLE_3M) and Adult/Pediatric Lifestyle Yearly Visits (P1_LIFESTYLE/ P2_LIFESTYLE) form. Different types of coverage are available for the US sites and Canadian sites. Participants are to check each type of insurance since some participants may have more than one type of coverage. Reference Card D may be used.

1.22.6 Income

The participant is asked the total annual gross household income, which is the amount BEFORE tax withholdings. Ranges of income are provided. The participant may decide not to answer. Reference Card E may be used.

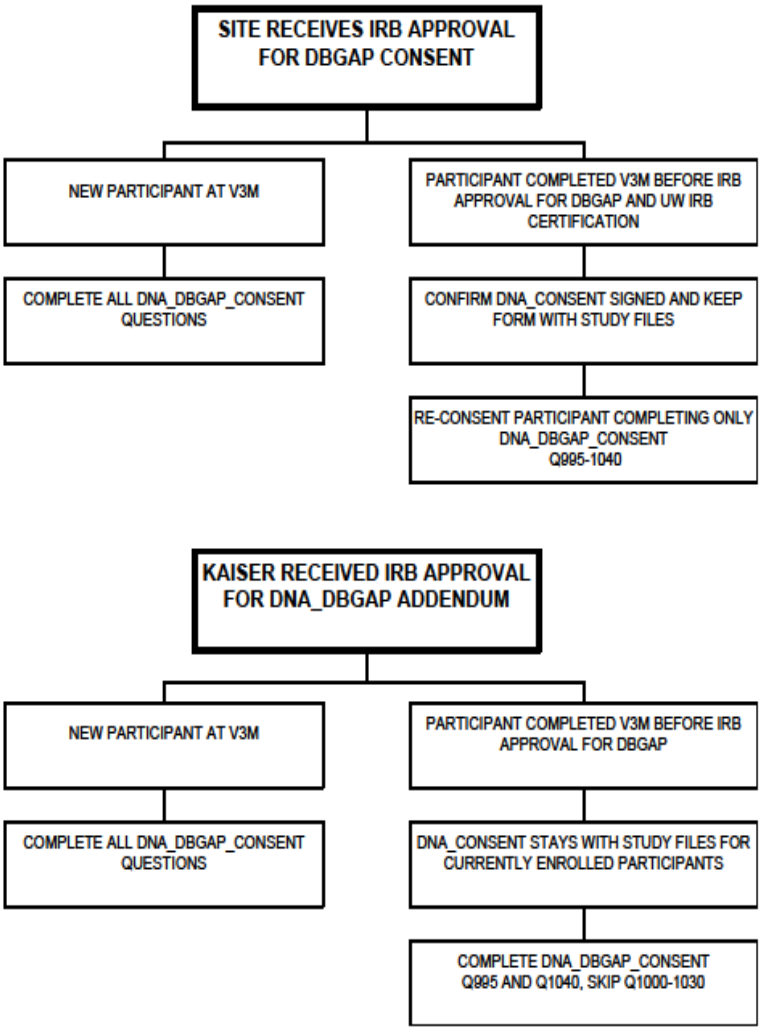
1.22.7 Completion of the Form

The Research Coordinator indicates if the participant or interviewer (or guardian for the pediatric participants) completed the form. The mode of administration remains the same throughout the completion of the form for that study contact. The Research Coordinator reviews each question of the form with the participant to assess intent and understanding of the questions, answers any questions, and evaluates completeness of the form prior to the end of the study visit.

1.23 DNA

1.23.1 Adult

The ASSESS-AKI Consortium will partner with the ASSESS AKI Central Laboratory for the extraction of DNA from samples obtained from the adult participants at Visit 3M for future genetic studies related to AKI and associated clinical outcomes. At the start of the Outpatient Phase, fresh whole blood was shipped to the Central Lab. The DNA is stored at -20C. On April 19, 2010, the transition from fresh whole blood to frozen packed cells (pellet) occurred. A genetic consent form for submission to dbGaP must be signed by the participant prior to completing the DNA_DBGAP_CONSENT form.



1.23.2 Pediatric

Frozen packed cells collected for DNA at the inpatient visit (Visit 0) are to be stored at the site until the completion of the 12-month visit (Visit 12M).

An ACD-A citrate tube is sent to the NIDDK Rutgers Biorepository. If the NIDDK Rutgers Biorepository is unable to create a cell line from the V12M sample, an attempt will be made at each yearly visit until the study ends. If no cell line is created, the frozen packed cells from V0 will be shipped to the Central Lab for DNA extraction. If the packed cells are not needed, the tube should be over labeled with a TRIBE label.

The Consortium will partner with the NIDDK Rutgers Biorepository to establish cell lines from the pediatric participants and with the Central Lab if the packed cells collected at V0 are used for the extraction of DNA .

Refer to the BIOSPECIMEN MOP.

1.24 ECG CENTRAL READING CENTER

EPICARE Contacts
Refer to the Electrocardiography Assessment Manual, the ASSESS-AKI Study.

1.25 ELECTROCARDIOGRAM (ECG)

1.25.1 Inpatient Phase

To provide a systematic comparison at the start of the study, at least one ECG obtained before or during the index hospitalization will be obtained for each adult participant and stored locally at each clinical research center.

1.25.2 Outpatient Phase

Prior to January 30, 2013, a 12-lead electrocardiogram will be obtained at Visit 3M and the yearly adult, in-person visits (Visits 12M, 24M, 36M) for all adult sites. After January 30, 2013, a 12-lead electrocardiogram will be obtained at Visit 3M and the yearly adult, in-person visits (Visits 12M, 24M, 36M, 48M, 60M, 72M, 84M) for the Kaiser and University of Washington sites.

After October 04, 2016, the following applies to all adult sites.

- Baseline ECG
  - All adult sites should make every effort to obtain an ASSESS-AKI ECG (either through their research center or send the participant to the ECG lab) or retrieve a clinically-obtained ECG from the participant's medical records. .
  - For participants who have already completed the V3M visit but in whom research personnel did not obtain a protocol-driven ECG at that time, clinical records from the site should be reviewed and a clinical ECG most proximate and preceding the V3M visit should be obtained. This ECG could be obtained during the V0 hospitalization or at an outpatient visit or during a hospitalization that is not more than 365 days prior to the V0 hospitalization. Preferably, an ECG nearest to the V0 hospital discharge date would be available and would be acceptable.
  - Baseline ECG is defined as an ASSESS-AKI ECG at V3M, a non-ASSESS ECG obtained during the V0 hospitalization, or at an outpatient visit or hospitalization that is no more than 365 days prior to the V0 hospitalization.
  - Baseline ECGs should be obtained for those who withdraw at or after V3M without a post-baseline ECG.
  - Baseline ECGs should be obtained for those who withdraw at or before V24M without a post-baseline ECG.
- Post-Baseline Visit ECG
  - In-center visits – all adult sites should obtain an ASSESS-AKI ECG for all visits (either through their research center or send the participant to the ECG lab), or retrieve a clinically-obtained ECG from the medical records within the follow-up window in each study year.
  - Home visits/Phone visits in lieu of in-center visits - all adults sites should attempt to obtain a mobile 12-lead ECG. If a mobile 12-lead ECG is not possible, the coordinator will know after the next phone contact if there was a hospitalization(s) or ER visit (P1_EVENTS, Q1000 = 1) and will ask if s/he has received a 12-lead ECG during the hospitalization or within the last six months. If the participant does not know if an ECG was completed, a quick search of the local EMR should be completed. After completing the HOSP_EVAL for the hospitalization(s), the coordinator will request an ECG as part of the medical records

request. If an ECG is not available from the medical records, the coordinator shall contact the provider where an ECG was completed within the last six months; this can be a hospital, clinic, or physician office. If no healthcare visits occurred in the prior six months, the ECG will be considered missing.

- Post-baseline visit ECG is defined as any ECG (ASSESS or non-ASSESS) obtained after V3M.
- Only one ECG should be obtained annually after the post-baseline ECG, and it should be collected at the annual visit or a hospitalization most proximate after the scheduled visit.

Example #1: V24 ECG is obtained. There is no ECG obtained at V36; no further action is needed at that time. At the next phone call visit, these are possible scenarios:

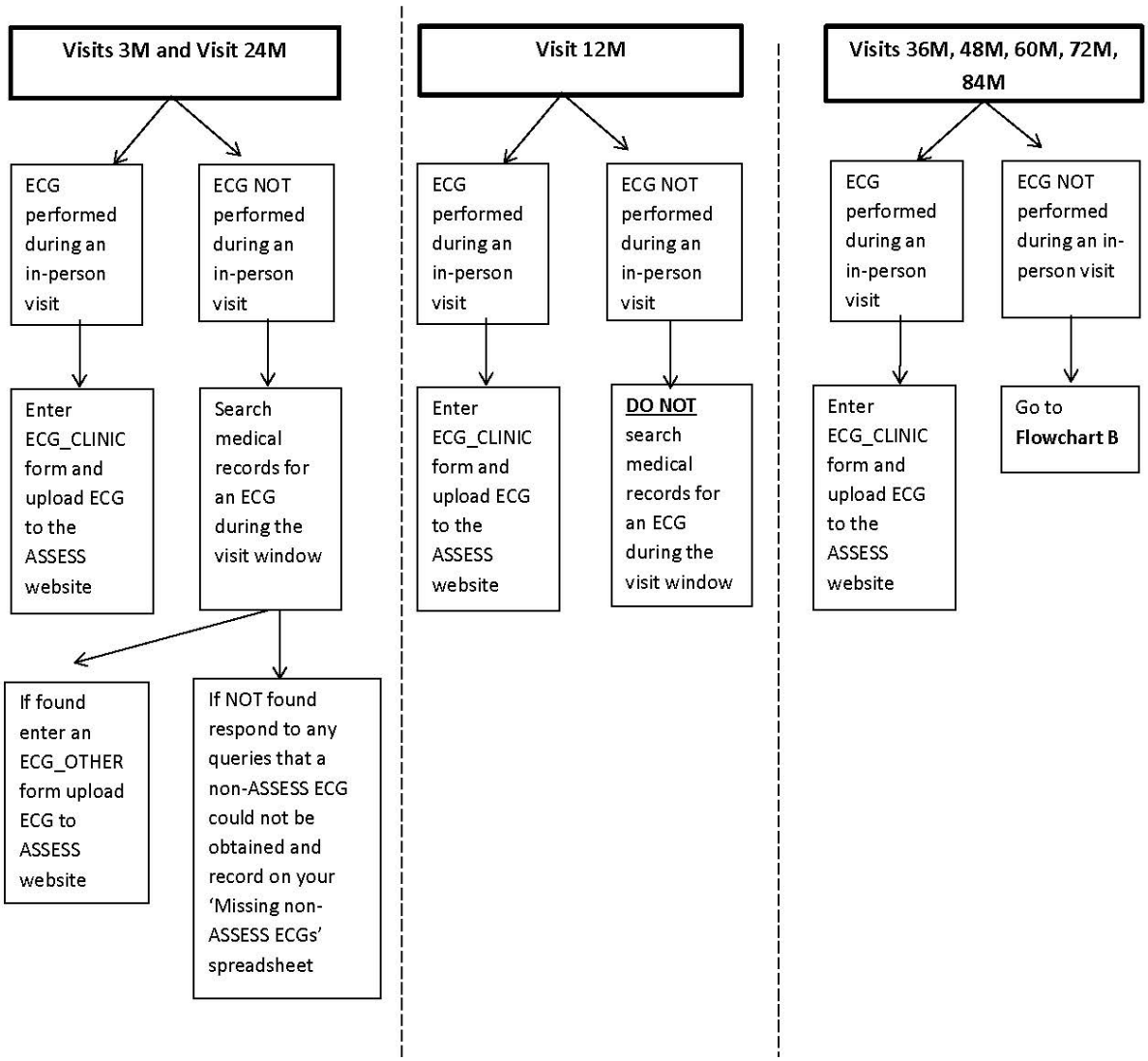
1) At V42 phone call, the participant indicates that s/he was hospitalized. The coordinator asks the participant if an ECG was done during the hospitalization or within the last six months. If an ECG was obtained, the coordinator will try to obtain it from the medical records or provider. If the ECG is available, complete the ECG_OTHER form, data enter the form, and keep the ECG stored at site. If s/he hasn't had an ECG or no ECG is available, no further action is needed.

2) At V42 phone call, the participant indicates that s/he was not hospitalized. The coordinator asks the participant if an ECG was done within the last six months. If yes, the coordinator shall contact the provider where an ECG was completed within the last six months. If the ECG is available, complete the ECG_OTHER form, data enter the form, and keep the ECG stored at site. If s/he hasn't had an ECG or no ECG is available, no further action is needed.

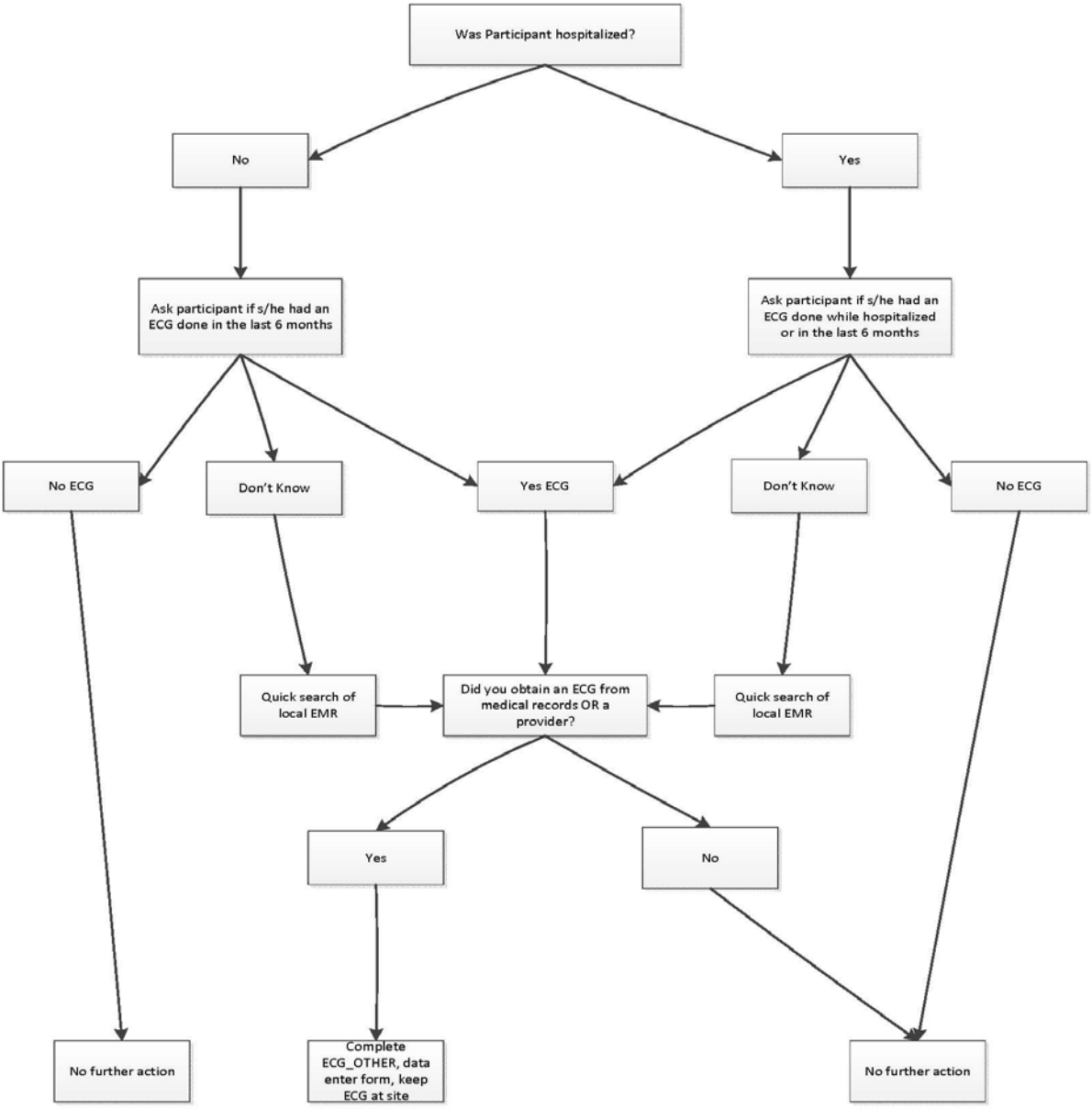
3) If the participant does not know if an ECG was completed, a quick search of the local EMR should be completed for the relevant time window.

Example #2: There is no ECG obtained prior to or at V3M. There is an ECG obtained at V36; this becomes the Post-Baseline ECG.

Flowchart A


Visits 3M and Visit 24M
ECG performed during an in-person visit
ECG NOT performed during an in-person visit
Enter ECG_CLINIC form and upload ECG to the ASSESS website
Search medical records for an ECG during the visit window
If found enter an ECG_OTHER form upload ECG to ASSESS website
If NOT found respond to any queries that a non-ASSESS ECG could not be obtained and record on your 'Missing non-ASSESS ECGs' spreadsheet
Visit 12M
ECG performed during an in-person visit
ECG NOT performed during an in-person visit
Enter ECG_CLINIC form and upload ECG to the ASSESS website
DO NOT search medical records for an ECG during the visit window
Visits 36M, 48M, 60M, 72M, 84M
ECG performed during an in-person visit
ECG NOT performed during an in-person visit
Enter ECG_CLINIC form and upload ECG to the ASSESS website
Go to Flowchart B

Flowchart B


Was Participant hospitalized?
No
Yes
Ask participant if s/he had an ECG done in the last 6 months
Ask participant if s/he had an ECG done while hospitalized or in the last 6 months
No ECG
Don't Know
Yes ECG
Don't Know
No ECG
Quick search of local EMR
Did you obtain an ECG from medical records OR a provider?
Quick search of local EMR
Yes
No
No further action
Complete ECG_OTHER, data enter form, keep ECG at site
No further action

If an ECG cannot be found, record your attempt on the spreadsheet, Missing non-ASSESS ECGs.

1.25.3. Posting ECGs to the ASSESS AKI website

To prevent sites from posting duplicate ECGs, the DCC has instituted the following process:

- Have sites verify what they plan to post is not a duplicate by checking the shipping logs on the website
- Have sites verify what they are posting matches the description
- DCC will verify what is posted matches what the description states
- DCC will review past shipping log to verify no duplicates
- DCC will batch ECGs and shipping log and send to EPICARE
- DCC will post shipping log to website for sites to review and use as reference

For more information, refer to the Electrocardiography Assessment Manual, The ASSESS-AKI Study.

1.26 ELIGIBILITY CRITERIA

There are three screenings of eligibility; two (Visit 0 and Visit 0B) during the inpatient phase and one (Visit 3M) during the outpatient phase.

1.26.1 Inclusion/Exclusion Criteria at Visit 0 (ELIG1A, ELIG1B)

Note that the criteria listed below are presented in the order they appear on the Eligibility Checklists.

1.26.2 Eligibility Checklist 1A (ELIG1A)

ELIG1A, Q1000: FOR KAISER, VANDERBILT, and UNIVERSITY OF WASHINGTON SITES: A baseline serum creatinine value (pre-op/outpatient/non-emergency test) from an IDMS lab within 7 to 365 days prior to hospitalization is *required* for eligibility. If an outside laboratory is using the Siemens/Dade Dimension or NOVA whole blood analyzer, the serum creatinine value may not be used and is not considered to be IDMS calibrated.

ELIG1A, Q1005: FOR YALE SITES: A baseline serum creatinine value (pre-op/outpatient/non-emergency test) within 365 days prior to surgery is *required* for eligibility.

ELIG1 A, Q1010: AKI participants who remain hospitalized 90 or more days after the AKI episode would be unable to complete an outpatient three-month study visit following the identification of the AKI episode. Check N/A for Non-AKI participants because they will not have an AKI episode.

ELIG1A, Q1020: Women who are actively pregnant or breastfeeding are not eligible. Check N/A if the participant is male. Check No if the participant is postmenopausal or premenarche female.

ELIG1A, Q1030: Prior chronic hemodialysis or peritoneal dialysis (lasting ≥ three months)

ELIG1A, Q1040: An estimated GFR < 15 ml/min/1.73m^2 not receiving renal replacement therapy. The latter eGFR cutoff will be used given that any additional AKI in the setting of very low GFR will be difficult to detect and has unknown clinical significance. An eGFR calculator is posted on the ASSESS-AKI website.

ELIG1A, Q1050: Calcineurin inhibitors, the mainstay of anti-rejection treatment in transplant patients, can cause significant fluctuations in serum creatinine concentration that are both hemodynamic in the acute phase and can reflect renal fibrosis in the chronic phase.

ELIG1A, Q1060: The myeloma kidney resulting in acute renal failure is a completely different phenotype from typical “hospitalized AKI” and leads to specific therapies (e.g., plasmapheresis).

ELIG1A, Q1070: AKI in the setting of hepatorenal syndrome is a result of severe renal vasoconstriction, is nearly always a diagnosis of exclusion, and potentially has a therapy including but not limited to splanchnic vasoconstrictors, transjugular intrahepatic portosystemic shunt, and liver transplantation.

ELIG1A, Q1080: Glomerulonephritis is a unique phenotype of AKI that primarily involves the glomerulus rather than the renal tubules, and also has specific anti-inflammatory therapies. The acute glomerulonephritis may be diagnosed clinically or by biopsy. However, if the participant has a biopsy during the index hospitalization with results obtained after enrollment demonstrating a specific pathologic diagnosis

not consistent with one of the exclusion criteria (e.g., a biopsy showing acute interstitial nephritis), the participant will remain eligible to continue in the study. Participants with lupus nephritis (if the glomerulonephritis is secondary and stable [not active]) and participants with alport's disease (if the glomerulonephritis is not more progressive than diabetes mellitus nephropathy) are eligible.

- The Research Coordinator should consult the site PI if any of these terms are in the medical records:

  - Any nephropathy outside of diabetic or hypertensive
  - Rapidly Progressive GN - another way of saying an aggressive inflammatory disease affecting the glomerulus
  - Crescentic GN - what it looks like under a microscope if you biopsy RPGN
  - Examples of GNs that can be acute:
    Lupus Nephritis
    Membranoproliferative GN (MPGN)
    Cryoglubin-associated GN
    ANCA-associated/pauci-immune GN (aka Wegener's, microscopic polyangiitis)
    Anti-glomerular Basement Memberane Disease (Anti-GBM)
    Acute IgA nephropathy (can also be chronic)
    myeloma kidney (should be an automatic exclusion)
    Fibrillary GN (can be acute)
    Immunotactoid GN (can be acute)
  - Other chronic gloerular diseases:
    Membranous nephropathy
    Focal segmental glomerulosclerosis (FSGS)
    Minimal Change Disease
    Amyloid
    Thin Basement Membrane Disease
    Alport's disease
    C1Q nephropathy

ELIG1A, Q1090: Acute urinary obstruction is a reversible form of acute kidney injury that has a specific therapy.

ELIG1A, Q1100: Hospitalization involving partial or total nephrectomy given that a rise in serum creatinine due to nephrectomy is not true "AKI" as approximately half of a person's total nephron mass was acutely removed.

ELIG1A, Q1110: These participants have a history of metastatic or systemic cancer AND are receiving active treatment. They will be unable to allow complete evaluation of the long-term impact of an episode of AKI. Non-metastatic lung or colon cancer is included. If the participant reports localized squamous cell carcinoma, check No.

ELIG1A, Q1120: These participants have a very high short-term mortality rate and will be unable to allow complete evaluation of the long-term impact of an episode of AKI.

ELIG1A, Q1130: These participants will be unable to allow complete evaluation of the long-term impact of an episode of AKI.

ELIG1A, Q1140: An active interventional study is defined as receiving a study intervention at the three-month visit regardless of intervention (e.g., pharmacological, mechanical, lifestyle, educational, etc.)

ELIG1A, Q1150: These participants will be unable to participate in the study within a home, community, or clinical setting.

ELIG1A, Q1160: If any of the shaded boxes are selected, the participant is ineligible. Stop the visit and complete the Withdrawal (WITHDR) form.

1.26.3 Eligibility Checklist1B (ELIG1B)

This eligibility form is optional for the clinical research centers to use as a final screening tool prior to the Visit 3M. This form is completed over the telephone when calling to confirm the Visit 3M appointment date and time.

The Eligibility 1B Script (ELIG1B_SCRIPT) should be used to facilitate the interview and completion of the checklist. See Section 2 for more information regarding the completion and entry of this form.

ELIG1B, Q1000: If the participant died prior to the three-month study visit, proceed to Q1080 and complete the Withdrawal (WITHDR) form and Death Record Evaluation (DEATH_EVAL) form.

ELIG1B, Q1010-1020: Prior chronic hemodialysis or peritoneal dialysis (lasting ≥ three months). If the participant expects to be on dialysis at the time of the three-month visit, he/she is not eligible.

ELIG1B, Q1030-1040: The participant cannot be enrolled in an active interventional study defined as receiving a study intervention at the three-month visit regardless of intervention (e.g., pharmacological, mechanical, lifestyle, educational, etc.).

ELIG1B, Q1050: These participants have a history of metastatic or systemic cancer AND are receiving active treatment. They will be unable to allow complete evaluation of the long-term impact of an episode of AKI.

ELIG1B, Q1070: Women who are actively pregnant or breastfeeding are not eligible. Check N/A if the participant is male. Check No if the participant is postmenopausal or premenarche female.

ELIG1B, Q1080: If any of the shaded boxes are selected, the participant is ineligible. Stop the visit and complete the Withdrawal (WITHDR) form.

1.26.4 Eligibility Checklist 2 (ELIG2)

This eligibility form is for the clinical research center to use as a final screening tool prior to enrollment in the outpatient phase and matching. This form is completed prior to performing any procedures (ECG) and collecting any blood and urine samples.

ELIG2, Q1000: Women who are actively pregnant or breastfeeding are not eligible. Check N/A if the participant is male. Check No if the participant is postmenopausal or premenarche female.

ELIG2, Q1005: AKI participants who remain hospitalized 90 or more days after the AKI episodes would be unable to complete an outpatient three-month study visit following the identification of the AKI episode. Check N/A for Non-AKI participants because they will not have an AKI episode.

ELIG2, Q1010: Prior chronic hemodialysis or peritoneal dialysis (lasting ≥ three months). If the participant is on dialysis at the time of the three-month visit, he/she is not eligible.

ELIG2, Q1020-1070: There is the possibility that additional information may become available during the interim period between the hospital discharge and the three-month visit. If it does, this new information should be incorporated into the completion of the ELIG2 form.

ELIG2, Q1020: Calcineurin inhibitors, the mainstay of anti-rejection treatment in transplant patients, can cause significant fluctuations in serum creatinine concentration that are both hemodynamic in the acute phase and can reflect renal fibrosis in the chronic phase.

ELIG2, Q1030: The myeloma kidney resulting in acute renal failure is a completely different phenotype from typical "hospitalized AKI" and leads to specific therapies (e.g., plasmapheresis).

ELIG2, Q1040: AKI in the setting of hepatorenal syndrome is a result of severe renal vasoconstriction, is nearly always a diagnosis of exclusion, and potentially has a therapy including but not limited to splanchnic vasoconstrictors, transjugular intrahepatic portosystemic shunt, and liver transplantation.

ELIG2, Q1050: Glomerulonephritis is a unique phenotype of AKI that primarily involves the glomerulus rather than the renal tubules, and also has specific anti-inflammatory therapies. The acute glomerulonephritis may be diagnosed clinically or by biopsy. However, if the participant has a biopsy during the index hospitalization with results obtained after enrollment demonstrating a specific pathologic diagnosis not consistent with one of the exclusion criteria (e.g., a biopsy showing acute interstitial nephritis), the participant will remain eligible to continue in the study. Participants with lupus nephritis (if the glomerulonephritis is secondary and stable [not active]) and participants with alport's disease (if the glomerulonephritis is not more progressive than diabetes mellitus nephropathy) are eligible.

- The Research Coordinator should consult the site PI if any of these terms are in the medical records:
    - Any nephropathy outside of diabetic or hypertensive
    - Rapidly Progressive GN - another way of saying an aggressive inflammatory disease affecting the glomerulus

- Crescentic GN - what it looks like under a microscope if you biopsy RPGN
- Examples of GNs that can be acute:
  Lupus Nephritis
  Membranoproliferative GN (MPGN)
  Cryoglubin-associated GN
  ANCA-associated/pauci-immune GN (aka Wegener's, microscopic polyangiitis)
  Anti-glomerular Basement Memberane Disease (Anti-GBM)
  Acute IgA nephropathy (can also be chronic)
  myeloma kidney (should be an automatic exclusion)
  Fibrillary GN (can be acute)
  Immunotactoid GN (can be acute)
- Other chronic gloerular diseases:
  Membranous nephropathy
  Focal segmental glomerulosclerosis (FSGS)
  Minimal Change Disease
  Amyloid
  Thin Basement Membrane Disease
  Alport's disease
  C1Q nephropathy

ELIG2, Q1060: Acute urinary obstruction is a reversible form of acute kidney injury that has a specific therapy.

ELIG2, Q1070: These participants have a history of metastatic or systemic cancer AND are receiving active treatment. They will be unable to allow complete evaluation of the long-term impact of an episode of AKI.

ELIG2, Q1080: These participants will be unable to allow complete evaluation of the long-term impact of an episode of AKI. This is determined by the participant's treating physician or the CRC principal investigator.

ELIG2, Q1090: An active interventional study defined as receiving a study intervention at the three-month visit regardless of intervention (e.g., pharmacological, mechanical, lifestyle, educational, etc.)

ELIG2, Q1100: These participants will be unable to participate in the study within a home, community, or clinical setting.

ELIG2, Q1110: The minimum amounts of blood collected are 10mL for adult participants. If the minimum amount is not collected, the participant is ineligible. If the minimum amount of adult blood is not collected samples are not entered into Biological Sample Tracking (BST). There is no minimum at V3M for the pediatric participants. If no pediatric blood is collected, the blood samples are not entered into BST.

ELIG2, Q1115: The minimum amounts of urine collected are 20mL for adult participants, and for pediatric participants, 1.6mL for diaper wearers and 5mL for non-diaper wearers. If the minimum amount is not collected, the participant is ineligible. If the minimum amount of adult urine is not collected, the samples are not entered into BST. If the minimum amount of pediatric urine is not collected, the samples are entered into BST as 'not collected'.

ELIG2, Q1120: If any of the shaded boxes are selected, the participant is ineligible. Stop the visit and complete the Withdrawal (WITHDR) form.

See section 2 of the ASSESS PROTOCOL MOP for more information on completing the Eligibility Checklist2 (ELIG2) form.

1.27 ENROLLMENT

The figure below summarizes the overall approach to selection of AKI and non-AKI participants and timing of the planned enrollment into the long-term ASSESS-AKI follow-up. This approach will be operationalized at each of the clinical research centers.

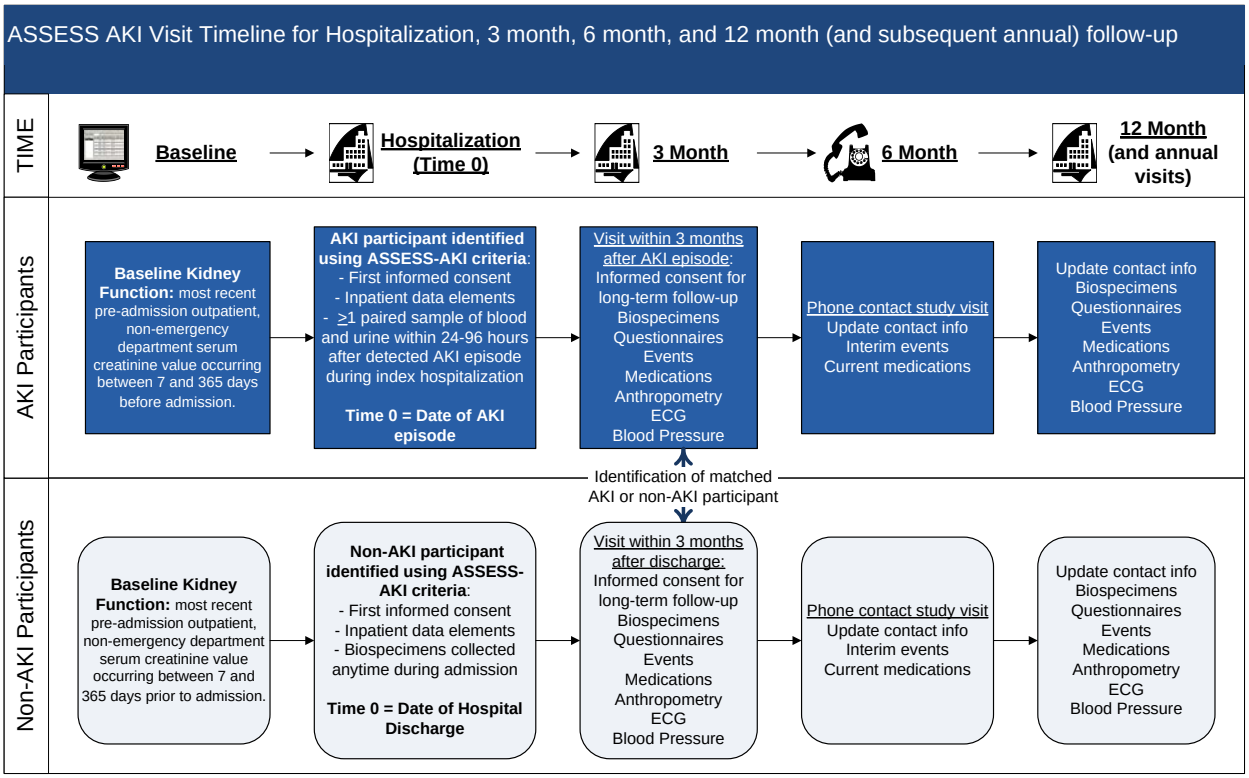


Figure 1. Summary of Identification and Enrollment Approach for AKI and Non-AKI Participants.

We will include 800 AKI and 800 matched non-AKI participants who officially enrolled into the long-term study, which is defined as completing the three-month study visit. It is important to note that Time Zero for an AKI participant is the date of the detected AKI episode that prompted initial enrollment, which includes obtaining at least one set of blood and urine specimens up to 96 hours after the AKI episode. For a non-AKI participant, Time Zero is the date of hospital discharge since there wasn't any relevant event during the index hospitalization to anchor to and because the hospital length of stay will likely be relatively short.

AKI participants will be enrolled in the outpatient study visit completed at three months after the AKI episode is recognized and non-AKI participants will be enrolled in the outpatient study visit completed three months after hospital discharge. Within 12 months of a completed three-month study visit, the AKI participant will be matched to a non-AKI participant or a non-AKI participant will be matched to an AKI participant, who will be targeted for study enrollment.

1.28 EQUIPMENT

Refer to the Equipment MOP
Refer to the Equipment MOP. Table approved by the QCC.

1.29 EVENTS

Events are defined as an unintended worsening in structure or functioning of the body or any experience suggesting a condition that is life-threatening or fatal or a condition that requires an emergency room visit, hospitalization, or test or procedure. An emergency room visit without an admission or lasting less than 23 hours and not resulting in death is not considered an event. A hospitalization lasting less than 23 hours and not resulting in death is not considered an event.

Events may have occurred since the last study contact (in-person visit or phone call). Some of the information collected is used to trigger the event adjudication process to further evaluate the co-morbidities with AKI.

The Research Coordinator should record the date of the participant's last study contact in the shaded box prior to the study contact. The participant is reminded of the date to keep the participant focused on the time period. If the participant reports a duplicate event, the event should be recorded only once. The coordinator can make a note in the progress notes that the participant recorded an event that was determined to be a duplicate report of the event.

Events after the index hospitalization include the following.

1.29.1 Adult Participants

- Death after the three-month visit (Visit 3M)
- Hospitalization/ ER visit
    - Admission to an inpatient rehabilitation unit or drug/alcohol treatment facility is not considered to be a hospitalization.
    - An emergency room visit without an admission or lasting less than 23 hours and not resulting in death is not considered an event.
    - A hospitalization lasting less than 23 hours and not resulting in death is not considered an event.
    - Cardiovascular
    - acute myocardial infarction; angina, unstable angina, angina pectoris; congestive heart failure; coronary artery by-pass surgery; heart arrhythmia; hemorrhagic stroke, intracranial hemorrhage; peripheral vascular disease; carotid artery disease;
    - Kidney
    - kidney transplant; hemodialysis; peritoneal dialysis;
    - Test or Procedures
    - surgery; balloon angioplasty; amputation of a limb due to blockage in the blood vessels in the arms, legs, or abdomen; carotid endarterectomy or balloon to open blockage in blood vessels in the neck; cardiac catherization
    - Other

1.29.2 Pediatric Participants

- Death after the three-month visit (Visit 3M)
- Hospitalization/ ER visit/ Intensive Care admission
    - Admission to an inpatient rehabilitation unit or drug/alcohol treatment facility is not considered to be a hospitalization.
    - An emergency room visit without an admission orlasting less than 23 hours and not resulting in death is not considered an event.
    - A hospitalization lasting less than 23 hours and not resulting in death is not considered an event.
- Cardiovascular
    - heart failure, pulmonary edema; hemorrhagic stroke, intracranial hemorrhage; peripheral vascular disease; cavopulmonary connection, fontan surgery, conduit replacement, mitral valve repair/replacement, aortic valve repair/replacement; acute myocardial infarction; angina, unstable angina, angina pectoris; coronary artery by-pass surgery; heart arrhythmia; carotid artery disease
- Kidney
    - kidney transplant; hemodialysis; peritoneal dialysis
- Sepsis
- Test or Procedures
    - cardiac catherization
- Other

Medical records will be examined to confirm the exact date for objective events (MI, hospitalization), but there will be those events for which the exact date will be unknown based on either missing or incomplete information.

Section D13.4 -13.5 of the ASSESS-AKI Protocol contains further descriptions of the above events.

1.29.3 Recording Events

Events that occur during the study are recorded on the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS) form. For each hospitalization, ER visit, test, and/or procedure performed, complete the Event Information Sheet (EVENT_INFO).

If it is discovered at or after Visit 6M that the participant has died as reported through proxy regardless of the location, refer to DEATH in the PROTOCOL SPECIFIC MOP. For more information, refer to the Event Adjudication Manual of Procedures.

For participants who answer Yes to Q1250 or Q1260 on the Adult Medical Event Questionnaire (P1_EVENTS) , you should complete a Procedure Investigation (PI). For participants who answer Yes to Q1350/Q1280 on the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS), you should complete the Outpatient Vascular Procedure Evaluation (OUTPT_VASC) form.

See Section 2 of the ASSESS PROTOCOL SPECIFIC MOP for more information on completing the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS), Event Information Sheet (EVENT_INFO), Withdrawal (WITHDR), and Death Record Evaluation (DEATH_EVAL) forms and if applicable, the Hospital/ER Record Evaluation (HOSP_EVAL),the Inpatient Creatinine (INPT_CREATININE), the ICD9/CPT Administrative Codes Sheet/ICD10/CCI Administrative Codes Sheet (ICD9_CPT_CODES/ICD10_CCI_CODES), Procedure Investigation (PI), Outpatient Vascular Procedure Evaluation (OUTPT_VASC), Outpatient Dialysis Evaluation (DIAL_EVAL) forms.

1.29.3.1 Outpatient Vascular Form

This form will be completed if percutaneous coronary intervention or cardiac catherization is reported on the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS) form.

For participants who answer Yes to Q1370/Q1320 on the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS) as having received dialysis,a course of dialysis (having a start/stop date) is counted as one when answering Q1390/Q1340 on the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS). You would also complete the Outpatient Dialysis Evaluation (DIAL_EVAL) form, which asks the start date of dialysis and if participant stopped dialysis and the date. Permanent dialysis is not marked as an event at each contact after qualifying as End Stage Renal Disease (ESRD). Dialysis in an inpatient rehabilitation unit should be considered as outpatient.

1.29.3.2 Outpatient Dialysis Evaluation form

This form is completed if dialysis is reported on the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS) form. Dialysis in an inpatient rehabilitation unit should be considered as outpatient.

1.29.3.3 AKI Evaluation form

On March 8, 2012, the QCC deleted the AKI_EVAL as an ASSESS data collection form. The QCC is agreeable with the sites data entering AKI_EVAL for events they've completed entirely. In addition, the QCC is agreeable with all sites not data entering the AKI_EVAL for events they are still in the process of collecting records, reviewing, and/or completing forms for reported events prior to March 8, regardless of the visit date.

1.29.4 Three-month Visit (Visit 3M)

At Visit 3M, a Medical History (P1/P2_MEDHX) is taken to probe for pre-existing conditions. This baseline knowledge is necessary to determine if conditions experienced during the study should be considered events (i.e., worsening of a chronic condition or a condition that appears for the first time during the study). Pre-existing conditions should not be recorded on the data collection forms, except as noted above, but they should be noted in the participant's clinic notes for future reference. At Visit 3M, only the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS) data collection form and Event Information Sheet (EVENT_INFO) administrative form are completed; the Hospital/ER Record Evaluation (HOSP_EVAL), Procedure Investigation (PI), Outpatient Vascular Procedure Evaluation (OUTPT_VASC), and Outpatient Dialysis Evaluation (DIAL_EVAL) forms are no longer being completed.

1.29.5 Outpatient Visits and Phone Contacts After the Three-month Visit (Visit 3M)

Follow up any events from previous visits and record any **new** events on the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS) form.

The only events that should be recorded are those that occurred since the last study contact (in-person visit or phone call).

Review the participant's file to determine if there were any events at the previous visit or if any new events were reported to clinic personnel between visits. If an ending date for an ongoing event is now known, update the Event Information Sheet (EVENT_INFO) form with the new information. Probe the participant/parent/guardian for the occurrence of any events that were not previously reported and record these on the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS) form.

1.30 EVENT ADJUDICATION

Event adjudication does not include the events recorded between Visit 0 and Visit 3M. Per the QCC minutes of April 12, 2012. a reviewer adjudicates the events that occur during a single hospitalization.

For more information, refer to the Event Adjucation Manual of Procedures.

Event Adjudication ended after twenty-two rounds on November 16, 2018.

1.31 HEIGHT and WEIGHT MEASUREMENTS

1.31.1 Measuring Tape

If a pediatric participant is a baby or toddler who cannot stand, supine length will be measured with a measuring tape.

1.31.2 Equipment

For more information, refer to the Equipment MOP.

1.31.3 Short Physical Exam

SEXAM, Q1090-1100: Leave fields blank for pediatric participants greater than 18 years of age.

1.32 HOSPICE

Follow-up with a participant admitted to hospice should be individualized, and the participant and the family should decide whether or not the participant will continue to be followed while in hospice. If the decision is to withdraw, the coordinator should record this in Q6000 of the Withdrawal (WITHDR) form to track. The coordinator may choose either "No longer willing to follow protocol/interested in participating "or Participant has personal constraints."

1.33 HOSPITALIZATIONS

Participants are asked at every study contact if they have been hospitalized or gone to the emergency room for any medical problem since the last ASSESS AKI study contact (in-person or phone). The number of ER visits and hospitalizations are recorded for each event on the Adult/Pediatric Medical Event Questionnaire (P1/P2_EVENTS) form. For each ER visit and/or hospitalization, the Event Information Sheet (EVENT_INFO) and a separate Hospital/ER Record Evaluation (HOSP_EVAL) form for each hospitalization are to be completed. An emergency room visit without an admission OR lasting less than 23 hours and not resulting in death is not considered an event. A hospitalization lasting less than 23 hours and not resulting in death is not considered an event.

If the participant goes to the Emergency Department (ED) and is admitted, the ED date is used as the admission date into the hospital for all ASSESS sites except for Yale Montreal, which does not include the ED date. Admission to an inpatient rehabilitation unit or inpatient drug/alcohol treatment facility is not considered to be a hospitalization.

If any ASSESS-AKI ICD-9/ICD-10 codes are identified in the hospital records, the ICD9_CPT_CODES or ICD10_CCI_CODES form should be completed. The ICD-9 and CPT codes may be found on the handout, ASSESS-AKI ICD-9 Diagnostic Codes. The ICD-10 and CCI codes may be found on the handout, ASSESS-AKI ICD-10 Diagnostic Codes. "In primary position only" refers to the primary discharge diagnosis position.

For all diagnoses other than arrhythmias, the general code is acceptable. For example: 433 for Occlusion and stenosis of intracerebral arteries, regardless of whether it is (433.1): Occlusion and stenosis of carotid artery or (433.2): Occlusion and stenosis of vertebral artery. For arrhythmias, the more specific codes should be used.

If no qualifying ICD-9/ICD-10 codes or codes for kidney transplant or arrhythmia are present, the coordinator records the primary discharge diagnosis in Q6000 on the HOSP_EVAL form, and the Principal Investigator completes Q1110-1160, Q1190-1240, and Q1260 and signs Q6000 to confirm who reviewed the chart.

HOSP_EVAL, Q1220: Non-traumatic amputation reflects vascular disease; in diabetes, it is often microvascular disease. It has to be more than one digit to be counted as an amputation.

If any qualifying ASSESS-AKI codes other than kidney transplant and arrhythmia are identified or any events checked in questions 1110-1160, Q1190-1240 of the Hospital/ER Record Evaluation (HOSP_EVAL) form, the event adjudication process should be initiated.

1.34 IMPAIRED COGNITIVE FUNCTION OR DEMENTIA

1.34.1 What forms should be completed during a visit?

A full visit should be attempted for participants with known dementia or impaired cognitive function. The use of a surrogate and/or EMR/claims databases is acceptable for obtaining information on selected case report forms and on potential clinical outcomes if your local IRB approves this approach. The coordindator should indicate in Q6000 on the form that the information provided is from the EMR or surrogate. Forms that specifically require the participant to complete (e.g., SF-12, TRAILS B, 3MS) should not be completed by a surrogate and should be set to missing with a comment describing why they are missing.

1.34.2 May samples be collected?

Samples may be collected if the visit occurs within the current consented period. You should ask your IRB about sample collection during the re-consent process.

1.34.3 May these participants be re-consented??

The site should work with its IRB during the follow-up phase on case-by-case exceptions for participants with known dementia or limited cognitive function to be able to follow the participants electronically or passively for potential clinical events.

1.35 INFORMED CONSENT

1.35.1 Regulatory Requirements for Informed Consent

The clinical research centers (CRCs) are responsible for recruiting participants and obtaining informed consents. The DCC is responsible for assuring that each local IRB has approved the protocol for a Consortium study and the procedures for recruitment, and has reviewed and approved the informed consent document. A Consortium study cannot begin at a CRC until that CRC has submitted IRB approval(s) to the DCC. Informed consent documents and signatures are retained at the CRCs. The CRCs will recruit participants by adhering to HIPAA regulations from "standing" populations at the CRCs by research, pharmacy and disease management databases, by referral from collaborating physicians, and by advertisement (flyers, brochures, posters, news media, etc).

An informed consent must be obtained from the participant BEFORE study information is collected or study procedures performed.

The DCC developed a template for the informed consent documents, which included the language required by the NIDDK Repository. The goal of the consent process is to establish and maintain procedures aimed at providing each potential participant with sufficient time and information to make informed decisions about participation in a Consortium study. The cornerstone for research on human beings is voluntary consent based on accurate information. The consent process is one of the more important participant-investigator activities because, if done properly, it serves not only to inform but also to bond the participant and the CRC. Moreover, the consent process that is employed in the Consortium is a continual process with continued education of participants about the study. Amendments to consent and re-consenting may be needed as additional important information becomes known to the Consortium. HIPAA authorization language is included, as necessary, in the confidentiality section of the informed consent form.

1.35.2 Administration of Informed Consent

Social Security Number

Potential participants will be asked to sign one or two informed consents depending on the CRC. YES/NO questions about providing a Social Security Number, permitting test results to be sent to a healthcare provider, and genetic testing are in the consent with signature requirements. If a participant is not comfortable about providing his/her social security number, explain to him/her how the number will be used and stored. Participants must respond to the YES/NO question in the ASSESS-AKI Informed Consent. Participants may decide to participate in the ASSESS-AKI study but not provide their Social Security Numbers. For all US participants, responses to the YES/NO questions about the use of the Social Security Number should be recorded in question 1 of the Social Security (SSN) form.

Genetic Testing

Participants may decide to participate in the ASSESS-AKI study but not the genetic testing. Explain the implications of participation in the genetic study and the selections contained in the YES/NO questions about genetic samples. Participants must respond to the YES/NO questions in the ASSESS-AKI Genetic

Sample Informed Consent. Responses to the YES/NO questions about genetic samples should be recorded in questions 1000-1030 of the DNA Consent (DNA_CONSENT) form.

The participant should be instructed to read the consent carefully and ask any questions or concerns that he/she has and to sign the consent only after his/her questions or concerns have been answered. Questions should be answered using lay language.

The participant should be given a copy of the signed informed consent form before the visit is over. You may need to ask the participant to sign two informed consents if a copier is not available so one signed copy may be given to the participant. Explain that he/she should contact the CRC or site should further questions occur after the visit.

Yale University

Yale University recruits potential participants prior to their cardiac surgery from the parent TRIBE-AKI study and approaching all adult subjects in the cardiothoracic intensive care unit who have had cardiac surgery on this admission for CABG, valve, or aneurysm. On day 3 or 4 of hospitalization, each participant is screened by research personnel for feasibility of long-term follow-up and asked for permission for future contact. Information on two additional contacts names/numbers is obtained at this time. All adult participants with AKI are contacted to schedule a three-month visit. At the three-month visit, study personnel obtain written consent for participation in the long-term study

Vanderbilt University

Once potentially eligible participants are identified from the ICU's, step down unit, and hospital floors at Vanderbilt including, but not limited to, those enrolled in the VALID parent cohort, research personnel enroll participants into the study and a copy of the informed consent is provided. Participants are given one week to consider the study before requesting the return of the informed consent.

Kaiser Permanente of Northern California

For AKI participants:

- Research personnel go to each recruiting hospital and after confirming access to the AKI participant, obtain written consent from the participant to complete a short questionnaire, obtain a single non-fasting blood specimen and random urine sample, and confirm the participant's agreement to be contacted within the next 30 days to discuss the study further.
- Within 30 to 45 days after hospitalization, a follow-up letter from the CRC PI is sent to each AKI participant enrolled during the acute hospitalization to introduce the long-term study protocol.
- One week after sending the letter, research personnel call the AKI participant to screen for remaining eligibility and to schedule the three-month visit.
- At the three-month visit (conducted at a central research clinic in Oakland), research personnel obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.
- Research personnel also review the consent at the 12-month follow-up visit to reinforce the schedule and study protocol with the participant.

For non-AKI participants:

- After an AKI participant successfully completes a three-month study visit, research personnel identify a pool of up to ten possible matched non-AKI participants who are hospitalized within a recent time frame of the enrolled AKI participant.
- Prior to hospital discharge, research personnel go to each recruiting hospital and after confirming access to the potential non-AKI participant, obtain written consent from the non-AKI participant to complete a short questionnaire, to obtain a single non-fasting blood specimen and random urine sample, and to confirm the participant's agreement to be contacted within the next 30 days to discuss the study further.
- Within 30 to 45 days after hospitalization, a follow-up letter from the CRC PI is sent to each non-AKI participant enrolled during the acute hospitalization to introduce the long-term study protocol.
- One week after sending the letter, research personnel calls the non-AKI participant to screen for remaining eligibility and to schedule the three-month visit.
- At the three-month visit, research personnel obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.
- Research personnel also review the consent at the 12-month follow-up visit to reinforce the schedule and study protocol with the participant.

University of Washington

The University of Washington will recruit 200 adult AKI participants and 200 matched adult non-AKI participants from the ICU's at Harborview Medical Center. Patients in the trauma, surgical, and medical ICU's will be screened daily for inclusion/exclusion criteria. We will seek IRB permission to initiate collection of samples before consent has been obtained. This will allow us to enroll patients who are too ill to provide consent but are without local surrogates. If consent is not obtained, these samples will be destroyed.

Patients/surrogates will be approached for possible consent into the ASSESS-AKI study on day 1 of their hospitalization. Upon this initial contact, we will ask for consent for participation in a short questionnaire, collection of study samples, and permission for further contact for long term aspects of the study. We will obtain additional contact names/numbers as well. We anticipate two possible scenarios for the consent process of study subjects.

Cohort 1:

For those patients with a pre-hospitalization creatinine within the past 365 days documented in the medical record, immediate enrollment into the study can occur. Sample collection will be initiated and serum creatinine data will be extracted from the electronic medical record to assess for the presence of AKI.

Patients in whom surrogate consent is obtained during hospitalization will need to provide informed consent by the three-month visit and efforts will be made to obtain consent before hospital discharge. Patients unable to provide informed consent by the three-month visit will be ineligible for the longitudinal study.

We anticipate that given the proposed matched parallel cohort design, we will be enrolling both AKI participants and non-AKI participants and will ultimately be matched on a minimal set of key confounding characteristics per study protocol.

Cohort 2:

For patients without a pre-hospitalization creatinine, we will ask for consent as noted above, and will additionally ask for signatures on a Release of Medical Information form so that primary care or referral providers may be contacted for potential creatinine values within the past year. If obtained, verification that creatinine values were obtained from IDMS-standardized laboratories will occur. Sample collection will be initiated. If creatinine values are unable to be determined, these subjects will not be contacted for the follow up portion of the study. If surrogate consent has been obtained, subjects will be re-consented before discharge and concurrently approached for consent to place their samples and data in the University of Washington KRI Data and Biosample Repository.

Within 1-3 weeks following discharge, materials will be mailed to all potential AKI and non-AKI participants enrolled during the acute hospitalization to introduce the long term follow up protocol. The mailing will include a thank you letter plus a flyer containing explanation of the long-term study. One week after mailing, research personnel will call eligible participants to answer potential questions, screen for remaining eligibility, and invite them to attend the three-month study visit.

At the three-month visit (conducted at the University of Washington KRI facilities and laboratory or in patient home), research personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.

1.36 INPATIENT CHECKLIST

If the information is in the PMH and the patient response differs from the PMH, you are to note what is in the PMH, and if the information is in one note, and not another note, count it as 'Yes'.

1.36.1 P1_INPATIENT CHECKLIST1

Q1020: The goal is to identify patients with coronary heart disease at study entry. For TRIBE-AKI patients undergoing CABG, they are classified as having coronary heart disease because they are having the revascularization before their AKI event for the purpose of treating coronary heart disease. Isolated valve surgery does not imply coronary heart disease.

Q1060: Refer to CHRONIC LUNG DISEASE in the PROTOCOL SPECIFIC MOP for examples.

Q1200: The date of AKI episode is the date that the participant first qualifies as AKI per our criteria.

Q1250: Family history of kidney disease does not include renal cancer. Examples of family history include dialysis, ESRD, transplant, and polycystic kidney disease.

Q1260-1370: Refer to Medication List for examples.

1.36.2 P1_INPATIENT CHECKLIST2

Q1000-1060: Refer to reference card, Medication List, for examples. If a combination medication is noted, mark 'Yes' for each drug class.

Q1090: Refer to CONTRAST GADOLINIUM in the PROTOCOL SPECIFIC MOP for examples.

Q1120: Mark Yes if the participant returned to the OR after the original surgery.

1.36.3 P2_INPATIENT CHECKLIST1

Q1030: Generalized hypertension, not pulmonary hypertension

Q1130: Previous heart surgeries include those surgeries before TRIBE AKI enrollment.

Q1300-1410: Refer to reference card, Medication List, for examples. If a combination medication is noted, mark 'Yes' for each drug class.

Q1420: This is for babies born with some cyanotic defects who get prostaglandins preoperatively to maintain a patent ductus ateriosus.

1.36.4 P2_INPATIENT CHECKLIST2

Q1000-1070: Refer to reference card, Medication List, for examples.

Q1130: Mark Yes if the participant returned to the OR after the original surgery.

Q1190: All pediatric participants from Montreal and Cincinnati sites are expected to have a RACHS category score from one to seven.

1.37 INPATIENT SERUM CREATININE MEASURES

Kidney function will be measured during any inpatient hospitalization, including the Visit 0 hospitalization and any hospitalization during the outpatient phase of the ASSESS-AKI study prior to the onset of ESRD.

A serum creatinine value will be collected for each day of the hospitalization up to 90 days. If the participant goes to the Emergency Department (ED) and then is admitted, the serum creatinine value collected in the ED is the first inpatient serum creatinine measure. If more than one value is present, record the peak value within the 24-hour period.

1.38 LABORATORIES, LOCAL and CENTRAL

For adult participants, the local laboratory will be used for the CBC collected during the outpatient phase.

For adult participants, the Central Lab will receive one 1.0mL aliquot of urine and one 1.0mL aliquot of serum for the core measurements during the outpatient phase.

For pediatric participants, the Central Lab will receive one 1.0mL aliquot of urine and one 0.5mL aliquot of plasma for the core measurements during the outpatient phase. If NIDDK Rutgers Biorepository is unable to establish a cell line, the frozen packed cells collected at the inpatient visit (Visit 0) will be sent to the Central Lab for DNA extraction.

The expected turnaround time for the core measurement faxed results is 7 to 10 days after receipt of the aliquots.

Advanced Research and Diagnostic Laboratory
ASSESS Study
1200 Washington Ave S, Suite 175
Minneapolis, MN 55415

For more information, refer to the BIOSPECIMEN MOP.

1.39 LIFESTYLE

1.39.1 Mode of Administration

The Adult/Pediatric Lifestyle Visit 3M (P1_ LIFESTYLE _3M/P2_LIFESTYLE_3M) and Adult/Pediatric Lifestyle Yearly Visits (P1_ LIFESTYLE /P2_LIFESTYLE) forms are intended to be administered by the Research Coordinator as a participant interview. Adult/Pediatric Lifestyle Visit 3M (P1_ LIFESTYLE _3M/P2_LIFESTYLE_3M) forms are administered during the three-month visit and the Adult/Pediatric Lifestyle Yearly Visits (P1_ LIFESTYLE /P2_LIFESTYLE) forms are administered during the yearly visits (12M, 24M, 36M, 48M, 60M, 72M, 84M).

Under the following conditions, a site may decide to mail the form to the participant for completion prior to the study visit or to administer the form as a phone interview:

- The mode of administration remains the same throughout the completion of the form for that study contact.
- The Research Coordinator reviews each question of the form with the participant to assess intent and understanding of the questions, be available to answer any questions, and evaluate completeness of the form prior to the end of the study visit.
- The condition of the form is not bent, torn, or stained to prevent scanning. If the condition of the form is unsatisfactory, the participant will be asked to complete another form during the study contact.

1.39.2 Smoking History

Participants will be asked about their past and present smoking history. Smoking includes cigarette, cigar, and tobacco pipe; chewing tobacco is not assessed in the study.

P1_LIFESTYLE_3M ,Q1110 -1120/ P2_LIFESTYLE_3M ,Q1170 -1180: The age when you started smoking a pipe and if you still smoke a pipe regularly are only asked on the Adult/Pediatric Lifestyle Visit 3M (P1_LIFESTYLE_3M/ P2_LIFESTYLE_3M) form.

If the pediatric participant is ten years of age or older, you may need to explain to the parent that you need to ask some routine social history questions in private for all patients 10 years and up. Most parents are expected to be ok with that. Let the pediatric participant know that his/her answer is confidential and you record the answer, even if you think s/he is not being truthful.

1.39.3 Alcohol Use

The frequency and amount of alcohol use is being assessed. Reference cards are available for the participant to facilitate understanding.

P1_LIFESTYLE_3M/P1_LIFESTYLE,Q1210: To be answered by men.

P1_LIFESTYLE_3M/P1_LIFESTYLE,Q1220: To be answered by women.

If the pediatric participant is ten years of age or older, you may need to explain to the parent that you need to ask some routine social history questions in private for all patients 10 years and up. Most parents are expected to be ok with that. Let the pediatric participant know that his/her answer is confidential and you record the answer, even if you think s/he is not being truthful.

1.39.4 Recreational Drug Use

These questions ask about the past and present use of marijuana, methamphetamines, cocaine, heroin, and other street drugs.

1.39.5 Health Insurance

Current health insurance and type of coverage are asked at each outpatient study visit on the Adult/Pediatric Lifestyle Visit 3M (P1_LIFESTYLE_3M/P2_LIFESTYLE_3M) and Adult/Pediatric Lifestyle Yearly Visits (P1_LIFESTYLE/P2_LIFESTYLE) forms. Different types of coverage are available for the US sites and Canadian sites. Participants are to check each type of insurance since some participants may have more than one type of coverage.

1.40 MATCHING CRITERIA

Each clinical research center (CRC) will pursue ideally a 1:1 ratio for AKI: Non-AKI participant matching for those enrolled into long-term follow-up. Unmatched participants will be put into a cluster rather than become a singlet. A matching non-AKI participant will be targeted to be enrolled within 12 months after an AKI participant is enrolled into the long-term follow-up (i.e., defined as completion of the 3-month study visit). Recruitment of a match is permitted in the opposite manner as well, i.e., a matching AKI participant will be targeted to be enrolled within 12 months after a non-AKI control is enrolled into the long-term follow-up.

See the discussion in *Section D.6.4* of the ASSESS-AKI Protocol for the rationale of the matching approach.

IF NO MATCH IS FOUND

If no match can be found, the AKI or non-AKI participant will be put into a cluster rather than continue in the study as a singlet.

IF A NON-AKI PARTICIPANT OR AN AKI PARTICIPANT DIES OR WITHDRAWS AFTER MATCHING

If an AKI participant or non-AKI participant dies or withdraws after matching and it is still within the six-month window of selecting a non-AKI participant, another AKI participant or non-AKI participant may be selected. If death or withdrawal occurs outside of this window, the AKI participant or non-AKI participant will continue to be followed. A new AKI participant or non-AKI participant will not be selected and matched.

1.40.1 Mandatory Matching Criteria

AKI and Non-AKI participants will be matched for the following three variables:

- Clinical Research Center (Kaiser, Yale, Vanderbilt, Washington)
- Baseline chronic kidney disease status (yes, no) using CKD-EPI estimated GFR threshold of <60 or ≥60 ml/min/1.73m^2
- Age group (adult, pediatric)

1.40.2 Additional Matching Considerations

To further reduce confounding, we will attempt to further match AKI and non-AKI participants for the following prioritized set of participant characteristics (Note: for pediatric *participants aged <18 years old being enrolled through TRIBE, no additional matching will be conducted because all non-AKI participants will be enrolled*).

- Prior cardiovascular disease (non-CVD, CVD).
- Prior diabetes mellitus (non-DM, DM). Diabetes mellitus will be defined as meeting one or more of the following criteria consistent with American Diabetes Association criteria:

  8.1 Preadmission physician diagnosis of diabetes mellitus

9.1 Participant self-report or medical record that participant is currently on any oral or injectable hypoglycemic agents (prior to index admission or upon initial follow-up visit)

10.1 Without a documented history in patients with suspected type 2 diabetes, the diagnosis can also be based on a fasting plasma glucose ≥ 126 mg/dL or symptoms of hyperglycemia (polyuria, polydipsia, and unexplained weight loss) and a casual outpatient plasma glucose ≥ 200 mg/dL prior to or upon follow-up blood work (one value of each criterion from separate days or two separate values of one of the criterion from separate days). Fasting is defined as no caloric intake for at least eight hours. Casual is defined as any time of day without regard to time since the last meal. No glucose measures during the index hospitalization will be used given that acutely ill patients can experience reversible hyperglycemia that is not due to underlying diabetes.

- Category of baseline estimated GFR (15-19, 30-44, 45-59, 60-89, 90-150 ml/min/1.73m^2)
- Adult age category (18-39, 40-49, 50-59, 60-69, 70-79, 80-89 years)
- Hospital location where AKI episode occurred (e.g., ICU, non-ICU)

A point system will be applied to assess the level of matching according to the secondary matching criteria. The points assigned for matching a non-AKI participant to an AKI participant range from 0 to 100 in the following manner:

1. Prior cardiovascular disease (non-CVD, CVD) – 30 points if the AKI participant and the non-AKI participant are within the same category, 0 points if the AKI participant and the non-AKI participant are not in the same category.
2. Prior diabetes mellitus (non-DM, DM) – 25 points if the AKI participant and the non-AKI participant are within the same category, 0 points if the AKI participant and the non-AKI participant are not in the same category.
3. Baseline eGFR categories (15-29, 30-44, 45-59, 60-89, 90-150) – 20 points if the AKI participant and non-AKI participant within the same category, 10 points if the AKI participant and the non-AKI participant are one category apart, and 0 points if the AKI participant and the non-AKI participant are two categories apart.
4. Age categories (0-17, 18-39, 50-59, 60-69, 70-79, 80-89) – 15 points if the AKI participant and non-AKI participant within the same category, 10 points if the AKI participant and the non-AKI participant are one category apart, 5 points if the AKI participant and the non-AKI participant are two categories apart, and 0 points if the AKI participant and the non-AKI participant are three or more categories apart.
5. Hospital location (non-ICU, ICU) – 10 points if the AKI participant and the non-AKI participant are within the same category, and 0 points if the AKI participant and the non-AKI participant are not in the same category.

1.40.3 Centralized Matching

At the end of each month, the DCC will generate a report for each site that lists the set of non-AKI participants, not previously matched, that are eligible to be matched to a specific AKI participant. This set of non-AKI participants will be ordered from highest to lowest with respect to the previously described 100-point matching score. The DCC will consult with each site prior to assigning the matches because the DCC information is based on data already entered into the database. The site may be aware of higher quality matches because of data that may not have been entered into the system at the time of discussion. This is expected to be a dynamic and ongoing nature of recruitment at each of the CRCs. For the adult participants, the Visit 0 packet and the required Visit 3M forms (Eligibility Checklist 2 [ELIG2], Adult Medical Event Questionnaire [P1_EVENTS], and Adult Medical History [P1_MEDHX]) should be data entered before an AKI participant or a non-AKI participant is matched. Unmatched participants will be put into a cluster rather than become a singlet.

1.41 MEDICAL HISTORY

1.41.1 Mode of Administration

The Adult/Pediatric Medical History (P1_MEDHX/P2_MEDHX) form is intended to be administered by the Research Coordinator as a participant interview.

Under the following conditions, a site may decide to mail the form to the participant for completion prior to the study visit or to administer the form as a phone interview:

- The mode of administration remains the same throughout the completion of the form for that study contact.
- The Research Coordinator reviews each question of the form with the participant to assess intent and understanding of the questions, be available to answer any questions, and evaluate completeness of the form prior to the end of the study visit.
- The condition of the form is not bent, torn, or stained to prevent scanning. If the condition of the form is unsatisfactory, the participant will be asked to complete another form during the study contact.

In addition to information on exclusion criteria, we will collect data on the following comorbid conditions based on medical records review and/or patient self-report:

- Malignancy other than non-melanoma skin cancer
- Chronic lung disease (chronic obstructive lung disease, reactive airway disease)
- Chronic liver disease (cirrhosis, chronic hepatitis)
- Rheumatoid arthritis
- Gout
- Systemic lupus
- Women's health (pregnancy, menopause, last menstrual period, hysterectomy)
- Renal history
- Vaccinations
- Systemic hypertension
- High cholesterol
- Diabetes mellitus (medication, retinopathy, neuropathy)

-

1.41.2 Visit 3M

If the information is in the PMH and the patient response differs from the PMH, you are to note what is in the PMH, and if the information is in one note, and not another note, count it as 'Yes'.

P1_MEDHX, Q1150: Ask if she has completed menopause prior to this visit AND enrollment in the study. The window is not limited to the period of time from index hospitalization to V3M.

P1_MEDHX, Q1175: Ask if she had a hysterectomy prior to this visit AND enrollment in the study. The window is not limited to the period of time from index hospitalization to V3M.

1.42 MEDICAL RECORDS

Before obtaining medical records, the CRC should secure a signed medical release form from the participant. The medical release forms should be stored separate from the study file.

Medical records will be used to complete the Inpatient Checklist 1 (P1/P2_INPATIENT1), Inpatient Checklist 2 (P1/P2_INPATIENT2), and the Eligibility Checklist 1A (ELIG1A) forms.

Medical records will be examined to confirm the exact date for objective events (MI, hospitalization), but there will be those events for which the exact date will be unknown based on either missing or incomplete information.

1.43 MISSED VISIT

Visits should be scheduled on the ideal visit date whenever possible or within the visit window. If a participant misses a visit, try to reschedule within the visit window.

If a situation arises where three-month visit (Visit 3M) cannot take place within the visit window, please contact the scientific coordinator at the DCC to request an exception prior to performing the interview or biomarker collection. A visit will be considered late if it occurs later than four weeks after the ideal date for the three-month visit (Visit 3M) or more than six weeks after the ideal visit date for the yearly in-person and phone contacts. A study contact is considered "missing" if it does not occur before the next study contact visit window opens.

Visits that occur before or after the visit window, except with Visit 3M, and any skipped visits need to be documented by the CRC. A spreadsheet is posted on the ASSESS website for each CRC to document these occurrences. The Visit Exceptions spreadsheets can be found on the ASSESS website, and the coordinator has access only to its site's spreadsheet. Refer to the Document Management MOP, Section 2 for more information on how to fill out the spreadsheet. There are also instructions in the Visit Window Exceptions folder under "How to Document Protocol Exceptions" and "How to Edit and Repost Visit Window Spreadsheet".

1.44 MODE OF ADMINISTRATION

Under the following conditions, a site may decide to mail the form to the participant for completion prior to the study visit or to administer the form as a phone interview:

- The mode of administration remains the same throughout the completion of the form for that study contact.
- The Research Coordinator reviews each question of the form with the participant to assess intent and understanding of the questions, be available to answer any questions, and evaluate completeness of the form prior to the end of the study visit.
- The condition of the form is not bent, torn, or stained to prevent scanning. If the condition of the form is unsatisfactory, the participant will be asked to complete another form during the study contact.
- This applies to the following forms:
    - P1_LIFESTYLE_3M/P2_LIFESTYLE_3M
    - P1_ LIFESTYLE /P2_LIFESTYLE
    - P1_MEDHX/P2_MEDHX
    - P1_OUTPT_DEMO/P2_OUTPT_DEMO
- These forms may be completed in addition to the ones above if a phone visit is conducted in lieu of an in-person visit:
    - CMED
    - CMED_OTC
    - P1_EVENTS/P2_EVENTS
    - MMMSE_PHONE. This is a phone version of the Modified Mini-Mental State Exam. Refer to the Quality of Life/Cognitive Function Manual for administering and scoring the phone version.
- Refer to 1.50 PHONE VISIT LIEU OF IN-PERSON VISIT

1.44.1 Completion of Visit While Hospitalized During the Outpatient Phase

Interviews during the Outpatient Phase may be completed while a participant is hospitalized if the site PI determines that the participant is clinically stable. If this is the situation, a protocol exception should be requested and the investigator's evaluation included with the request.

1.44.2 Completion of Forms

For any child less than 12 years old, only the parent is required to complete the forms (whether the questionnaire is filled out on the phone, in person, or mailed). For ages 12 to 17 years, the parent and child should be at least present when completing the forms. Adult participants (≥ 18 years) complete the forms.

1.45 MODIFIED MINI-MENTAL STATE EXAM

Cognitive function assessment will be measured by the Modified Mini-Mental Status Examination (3MS). The 3MS will be conducted during the 3-, 12-, and 36-month, adult, in-person visits, although it can also be conducted by telephone in participants who are not able to complete an in-person study visit. We also note that cognitive function will not be performed in enrolled pediatric participants as the 3MS is not possible to administer reliably in these participants.

Place the sentence writing and drawing in the participant file.

Refer to the Quality of Life/Cognitive Function Manual for administering and scoring the Modified Mini-Mental State Exam.

1.46 NON-AKI PARTICIPANT SELECTION

The CRC will identify and enroll a sample of hospitalized patients who did not appear to suffer an AKI episode and who are matched on a minimal set of key confounding characteristics. The number of non-AKI participants is capped at three per AKI participant.

1.46.1 Definition of Non-AKI, Adults

For adult participants, non-AKI status will be defined as < 20% relative increase AND absolute increase ≤ 0.2 mg/dL (17 umol/L) in peak inpatient serum creatinine compared with baseline outpatient serum creatinine.

1.46.2 Definition of Non-AKI, Pediatric

For pediatric participants, non-AKI status will be defined as < 50% relative increase in peak inpatient serum creatinine compared with baseline outpatient serum creatinine.

1.47 PARTICIPANT ASSENT

1.47.1 Acquire Participant Assent

Verbal assent for participants less than seven (7) years of age and written assent for those between seven and 17 years of age must be obtained for the ASSESS-AKI study before any study information is collected or any study procedures are performed.

Provide the participant a copy of the ASSESS-AKI study participant assent form and ask him or her to read it thoroughly. The participant should not sign the form until he or she has discussed its contents with you. Allow ample time for the participant to read the participant assent form thoroughly. If the participant is unable to read the assent form or seems to be struggling, offer to read it to him or her or to help with the more difficult sections. Be prepared to answer any questions the participant may have. If the person does not appear to understand the study or what participation entails, or if he or she has any other doubts about enrolling, do not ask him or her to sign the participant assent form.

Maintain the participant written assent form in the participant's study folder. To ensure confidentiality, do not send this form to the DCC. This document will be reviewed for its existence and integrity during data quality site visits.

1.48 PARTICIPANTS WHO RELOCATE

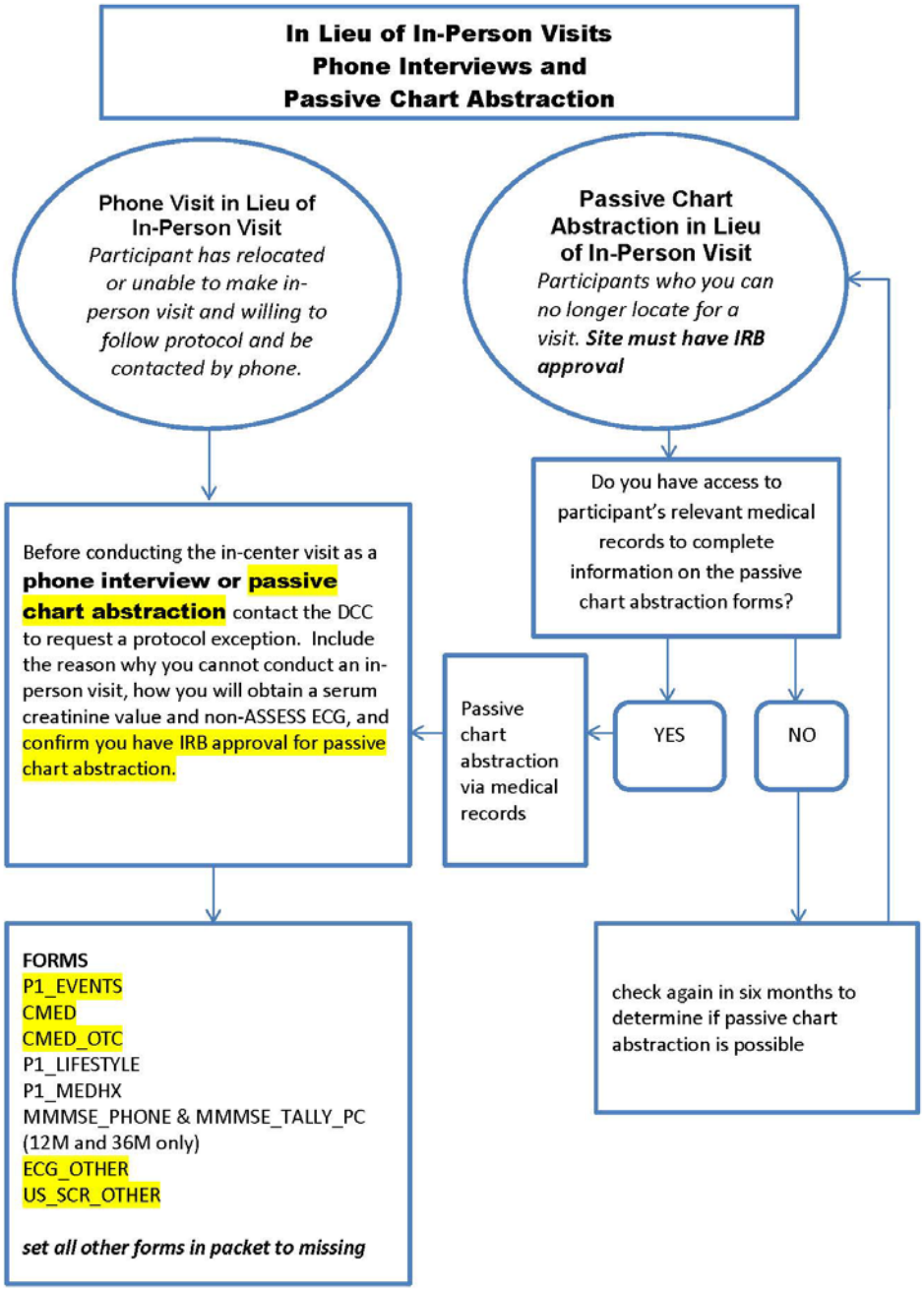
Participants who relocate to an area where they can no longer travel to a Clinical Research Center will be asked if study personnel may contact them annually for a telephone contact to complete the in-person forms. Not all of the forms or questions may be answered over the telephone and those should be set to missing. For example, the blood pressure form would not be completed and therefore, would be set to missing.

If the participant relocates in proximity to another ASSESS site, refer to the document, "Relocation of Participant General Procedure," which is posted on the website.

For participants who have relocated to an assisted living facility, confirm with the site PI that s/he does not have any concerns with the participant continuing in the study and send a protocol exception request to the DCC Scientific Coordinator.

1.49 PASSIVE CHART ABSTRACTION

1.49.1 Passive Chart Abstraction Schematic



1.49.2 Protocol Exception Request Guidelines

- Always copy the DCC administrative Assistant. In case the DCC Scientific Coordinator isn't available, the administrative assistant will forward it to the DCC PI.
- In the subject line of the email, you should include the Participant ID, visit date, and abbreviated reason (such as visit outside of the V3M window, phone visit instead of in-person visit, no urine collected, etc.). An example is "1-2A-1234 protocol exception V3M outside of the visit window."
- Include one exception request per email to aid with tracking and requests for more information.
- Include dates of lower and upper visit window if requesting visit outside of V3M window.
- If request is to conduct an in-person visit during a hospitalization, include the dates of the visit and discharge and the reason for the hospitalization.
- For in-person visits conducted as phone visits, explain the rationale and address how you plan to obtain sCr values and non-ASSESS ECG (except for V12M).

1.49.3 Approval for Passive Chart Abstraction

Status of IRB Approval for Passive Chart Abstraction

Site	Status	Notes
Kaiser	Yes	If not withdrawn
Vanderbilt	Yes	If not withdrawn
Yale - Cincinnati	Yes	If not withdrawn
Yale - Montreal	Yes	If not withdrawn
Yale - New Haven	Yes	Up to V48, if not withdrawn. If consented for phase 2, up to V90, if not withdrawn.
Yale - Ontario	Yes	If not withdrawn
University of Washington	Yes	If not withdrawn

1.50 PEDIATRIC QUALITY OF LIFE INVENTORY (PedsQL)

The Pediatric Quality of Life Inventory (PedsQL) 4.0 is a modular instrument that assesses health related quality of life in children and adolescents ages 2 to 18. It is a short questionnaire, consisting of 23 core questions that address physical functioning, emotional functioning, social functioning, and school functioning. The four Generic Core Scales are multi-dimensional child self-report and parent proxy-report and measure. For each aspect of health, participants are asked to rate how much of a problem five or eight items have been in the past 30 days.

The questionnaire varies slightly among the four age groups: young children (ages 5 to 7), children (ages 8 to 12), and adolescents (ages 13 to 18). It is also administered to parents of children ages 2 to 4 years (toddlers), young children (ages 5 to 7), children (ages 8 to 12), and adolescents (ages 13 to 18). Participants respond using a five-point scale to rate how much of a problem an item has been with 0 indicating never a problem, 1 is almost never a problem, 2 is sometimes a problem, 3 is often a problem, and 4 almost always a problem. For children ages 5 to 7, a scale of smiley faces replaces the numerical scale.

For more information, refer to http://www.pedsql.org/about_pedsql.html.

The PedsQL license number is 10666 and the expiration date is 06-2018.

1.51 PHONE VISIT LIEU OF IN-PERSON VISIT

Before conducting the visit as a phone interview, contact the DCC Scientific Coordinator to request a protocol exception. In your request, include the reason why you cannot conduct an in-person visit and how you will obtain a serum creatinine value. For adult participants, also include how you will obtain a non-ASSESS ECG. If a serum creatinine vaue and/or non-ASSESS ECG cannot be obtained, record your attempt on the Missing sCR_Other spreadsheet and/or the Missing non-ASSESS ECGs spreadsheet located on the ASSES website.

This does not include V3M.

After V6M, the following forms may be completed with adult participants.
P1_EVENTS
CMED
CMED_OTC
P1_LIFESTYLE
P1_MEDHX
MMMSE_PHONE for V12M and V36M only. This is a phone version of the MMMSE and there is also a phone version of the tally form, MMMSE_TALLY_PC.

After V6M, the following forms may be completed for pediatric participants.
P2_EVENTS
CMED
CMED_OTC
P2_LIFESTYLE
P2_MEDHX

In addition to the forms listed above, you would also enter the following forms.
ECG_OTHER – adults only
MMMSE_TALLY_PC – adults only
SCR_OTHER

At the time of data entry, adult site coordinators would set to missing the following forms.
TRAILSB_SCORE (add to missing TRAILS B Sheet)
SF-12
BLOOD_PRESSURE
SEXAM
P1_OUTPT_COLLECT_BLOOD
P1_OUTPT_COLLECT_UA
P1_OUTPT_PROCESS
DIPSTICK
DIPSTICK_RPT (Mark 'No' during entry)

At the time of data entry, pediatric site coordinators would set to missing the following forms.
BLOOD_PRESSURE
SEXAM
P2_V12M_COLLECT_BLOOD
P2_ V12M _COLLECT_UA

P2_ V12M _PROCESS
P2_OUTPT_COLLECT_BLOODP2_OUTPT_COLLECT_UA
P2_OUTPT_PROCESS

The following single forms would not be entered.
ECG_CLINIC
P1_OUTPT_COLLECT_BLOOD_2
P1_OUTPT_COLLECT_UA_2
P1_OUTPT_PROCESS_2
CAN_LABCBC/ US_LABCBC
DNA_DBGAP_CONSENT
PedsQL
P2_ V12M _COLLECT_BLOOD_2
P2_ V12M _COLLECT_UA_2
P2_ V12M _PROCESS_2
P2_OUTPT_COLLECT_BLOOD_2
P2_OUTPT_COLLECT_UA_2
P2_OUTPT_PROCESS_2
DIPSTICK
DIPSTICK_RPT
CAN_LABCBC/ US_LABCBC
DNA_CONSENT

1.52 PREGNANCY TESTING

Pregnancy tests will not be performed for female participants of child-bearing potential. The study will rely on self-report at the time of eligibility.

1.53 PROTOCOL VIOLATIONS, EXCURSIONS, and EXCEPTIONS

1.53.1 Protocol Violations

Protocol violations are defined as departures from accepted research practices, study protocol, and/or ASSESS-AKI methods of procedure that pose a risk to participant safety, adversely affect data quality, significantly affect the integrity of the major scientific goals of the study, and/or involve a significant and repeated breach of participant's privacy. By the nature of their definition, protocol violations are considered the most serious class of departure from the study protocol. All protocol violations will be reported to the center PI and the Quality Control Committee.

Protocol violations include (but are not limited to):

Eligibility Examples

- No baseline serum creatinine
- < 1 month old or >89 years old
- Exclusionary medical condition or therapy
- Pregnant or nursing
- Hospitalized ≥ 90 days after the AKI episode
- Did not consent at Visit 0 or Visit 3
- Parent did not consent; child (≥ 7 yo) did not give assent
- Incarcerated, institutionalized

Confidentiality Examples - 2nd time

- Contact information, Informed consent, and/or Registry form sent to DCC
- Identifying information sent to DCC or other groups/vendors

Source Documentation Example

- Baseline serum creatinine form was not signed by a second individual

Specimen Examples

- Minimum amount of blood was not collected and the adult was not withdrawn
    - Adults = 3 aliquots (0.5mL) EDTA plasma at Visit 0
    - Adults = 10mL whole blood at Visit 3M
- Minimum amount of urine was not collected and the adult was not withdrawn
    - Adults = 3 aliquots (1mL) at Visit 0
    - Adults = 20mL at Visit 3M
- Minimum amount of plasma was not collected at Visit 12M and the pediatric participant was not withdrawn

  - Peds = 0.175mL

- Minimum amount of urine was not collected and the pediatric participant was not withdrawn
  - Peds = 1.6mL for diaper wearers and 5mL for non-diaper wearers at Visit 3M
  - Peds = 1.6mL for diaper wearers and 5mL for non-diaper wearers at Visit 12M
- V0 samples collected >96 hours after the AKI event
- Samples were not collected
- Misplaced/loss of samples
- Samples not stored in -80°C freezer
- Required forms not data entered PRIOR to shipping – 2nd time
- Urine or blood samples drawn after participant deemed ineligible – 2nd time
- DNA sample drawn after participant deemed ineligible – 2nd time
- DNA sample drawn without DNA consent

Miscellaneous

- Consent form, deemed invalid by a Center's/Site's local IRB, is used
- Center/Site fail to obtain informed consent appropriately
- Participant withdrawn from study and forms continue to be completed for other visits

1.53.2 Protocol Excursions

Protocol Excursions are defined as departures from a study protocol or ASSESS-AKI methods of procedure that do not pose a risk to participant safety and do not adversely affect data quality or the integrity of the major scientific goals of the study, AND do not involve a significant and repeated breach of participant privacy.

If certification-related excursions persist at a given center or site and an uncertified individual continues to carry out study procedures without proper ASSESS-AKI training, serious effects on data quality may result. Such a scenario leads to the possibility of protocol violations being assigned. Likewise, if an outdated version of a form used by a center in error references incorrect study eligibility criteria, protocol violations may be assigned. These situations will be reviewed and classified on a case-by-case basis by the protocol's Scientific Coordinator, a member of the DCC, in consultation with the Quality Control Committee.

If a given center or site allows identifying information to be sent to the DCC, Lab, or any other ASSESS-AKI-affiliated group on more than one occasion, this repeated breach of privacy will be tracked as a protocol violation, in addition to the individual protocol excursions. Each time two new protocol excursions accrue in the category of "blinding of identity," a new protocol violation will be assigned in this category.

If a given center or site experiences a high frequency of protocol excursions in a specific area, the DCC and/or Quality Control Committee will address this issue with the PI of the center or site in an effort to resolve the problem.

Protocol excursions include (but are not limited to):

AKI participant/non-AKI participant Assignment

- Enrolled inappropriately as AKI participant/non-AKI participant
- Enrolled and is neither a AKI participant nor a non-AKI participant

Certification Examples

- Coordinator without certification completed form(s)

Confidentiality Examples – 1st time

- Contact information, Informed consent, and/or Registry form sent to DCC
- Identifying information sent to DCC or other groups/vendors

Source documentation

- Misplaced/loss of data/data collection forms

Specimen Examples

- Urine or blood samples drawn after participant deemed ineligible
- DNA sample not drawn after participant consented
- DNA sample drawn after participant deemed ineligible
- Samples not processed within 6 hours
- Sample collected after in-person visit
- At V3M, protease inhibitor not added to urine sample that is > 30 mL
- At V3M, protease inhibitor tablet added to urine sample that is < 30 mL
- Blood not sent to local lab for CBC– adult participants only
- Samples not sent to Biorepository
- Samples not sent to Central Lab for core measurements
- Samples sent to incorrect destination

Miscellaneous Examples

- Administration (interview vs. self-administered) varies within a single data collection form
- Administration of a form varies among visits
- Center/Site uses an outdated version of a data collection form
- Physical exam not performed
- Mistimed procedures (performing a lab test or interview outside of the window)

1.53.3 Protocol Exceptions

Occasionally a center or site will screen a participant or enroll a participant and find that he or she meets all but one of the eligibility criteria (e.g., the participant was hospitalized for 91 days after the AKI episode and there were extenuating circumstances). In such cases the Research Coordinator may contact the Scientific

Coordinator at the DCC for a protocol exception. Depending on the nature of the request, the Scientific Coordinator may consult with the Quality Control Committee for the protocol or an appropriate primary investigator for an ancillary study before a final decision is reached and communicated to the center. Exceptions that are requested and granted by the DCC before any action is taken by the center are tracked in a Protocol Exceptions spreadsheet, distinct from protocol violations and protocol excursions.

If an adult participant is anuric (i.e., unable to produce the 3mL of urine during the inpatient stay) due to AKI, the participant will not be excluded from the study. The site coordinator should contact the DCC Scientific Coordinator for an exception.

Before conducting an in-center visit as a phone interview or passive chart abstraction, request a protocol exception. Refer to Section 1.49 PASSIVE CHART ABSTRACTION.

The following are some guidelines for submitting a protocol exception request to expedite the process:

- Always copy the DCC administrative Assistant. In case the DCC Scientific Coordinator isn't available, the administrative assistant will forward it to the DCC PI.
- In the subject line of the email, you should include the Participant ID, visit date, and abbreviated reason (such as visit outside of the V3M window, phone visit instead of in-person visit, no urine collected, etc.). An example is "1-2A-1234 protocol exception V3M outside of the visit window."
- Include one exception request per email to aid with tracking and requests for more information.
- Include dates of lower and upper visit window if requesting visit outside of V3M window.
- If request is to conduct an in-person visit during a hospitalization, include the dates of the visit and discharge and the reason for the hospitalization.
- For in-person visits conducted as phone visits, explain the rationale and address how you plan to obtain serum creatinine values and non-ASSESS ECG (excluding V12M).

If a center or site fails to request an appropriate exception and instead proceeds with participant enrollment on its own judgment, a protocol violation or protocol excursion will be assigned as follows. If the DCC identifies a problem with participant eligibility criteria when the data are submitted, and no documentation of an approved exception exists, the issue will be referred to the Scientific Coordinator for review. If the exception ultimately is allowed, then necessary data corrections will be made to the database and the failure of the center or site to obtain prior approval will be tracked as a protocol excursion. If the exception is not allowed, the participant will be considered ineligible and a protocol violation will be assigned. Participants who have not been enrolled at the time when their ineligibility is discovered will be terminated from the study. Participants who have already been enrolled may be allowed to continue at the discretion of the center PI, an additional primary investigator for the protocol, and the Quality Control Committee.

In reference to protocol exceptions requested for Visit 3M window extensions to avoid a mistimed procedure, sites should request these prior to performing the interview or biomarker collection. Sites should adjust interview times within the preferred windows (See PROTOCOL SPECIFIC MOP, Appointments) as much as possible to maintain these time points. Visits that occur before or after the visit window, except with Visit 3M, and any skipped visits need to be documented by the CRC. A spreadsheet is posted on the ASSESS website for each CRC to document these occurrences.

The Visit Exceptions spreadsheets can be found on the ASSESS website, and the coordinator has access only to its site's spreadsheet. Refer to the Document Management MOP, Section 2 for more information on how to fill out the spreadsheet. There are also instructions in the Visit Window Exceptions folder under "How to Document Protocol Exceptions" and "How to Edit and Repost Visit Window Spreadsheet".

1.54 PROTOCOL VIOLATION REBUTTAL PROCESS

See Protocol Violation Rebuttal Process, in the GENERAL MOP for more information.

1.55 RECRUITMENT

1.55.1 Yale University

Yale will recruit 200 AKI participants and 200 non-AKI participants prior to their cardiac surgery from the parent TRIBE-AKI study and approaching all adult subjects in the cardiothoracic intensive care unit who have had cardiac surgery on this admission for CABG, valve, or aneurysm. The current plan is 300 adults and 100 children. On day 3 or 4 of hospitalization, each participant will be screened by research personnel for feasibility of long-term follow-up and asked for permission for future contact. Information on two additional contacts names/numbers will also be obtained at this time. If the participant agrees to long-term follow-up, the following steps will be initiated.

(1) Every month, a Co-Investigator will query the "TRAILSB" on-line database for all participants with AKI and all eligible non-AKI participants matched for the pre-specified criteria with the index participant with AKI.

- Eligible participants with non-AKI will be "ranked" for each in order from best match to worst match for each participant with AKI in the new time period.

(2) Materials to be mailed to all potential AKI and non-AKI participants considered eligible for long-term follow-up will be prepared approximately one month before the three-month visit. The mailing will include a thank you letter, tri-fold flyer containing explanation of the long-term study, and a "Certificate of Appreciation."

(3) One week after the mailing, research personnel at each site within TRIBE-AKI will call eligible participants.

- All adult participants with AKI will be contacted, unless targets for spectrum of severity are lagging (see Protocol, *Section D.5*), in which case only higher spectrum of severity AKI participants will be contacted and enrolled.
- In order to enrich the number of participants with severe AKI, additional possible AKI participants for ASSESS-AKI will be identified by screening the cardiothoracic intensive care unit at the participating TRIBE-AKI sites for patients who experience clinical AKI after undergoing cardiac surgery or aneurysm repair. These patients will be approached on the day their serum creatinine concentrations meet AKIN Stage 1 criteria. They will be asked by our coordinators about their willingness to participate in the ASSESS-AKI study. If they agree, then they will be enrolled into TRIBE-AKI. Their enrollment status will be entered into our online database.
- Adult participants will be contacted in order from highest number of matching criteria to lowest until the participant is secured for a three-month visit.
- Participants will be given a choice of follow-up at the research clinic or in their home.
- At the three-month visit, study personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.
- All children, of both AKI and non-AKI status, who agree to long-term follow-up, will be identified, contacted, and followed.

1.55.2 Vanderbilt University

Vanderbilt will recruit 250 adult AKI participants and 250 matched adult non-AKI participants from the ICU's, step down unit, and hospital floors at Vanderbilt and the local VA Medical Center (Tennessee Valley Healthcare System – Nashville Campus) including, but not limited to, those enrolled in VALID. All ICU patients will be screened daily. Patients meeting inclusion/exclusion criteria outlined in the protocol will be enrolled into the study based on assessment to AKI versus non-AKI status. Serum creatinine data will be extracted from the electronic medical record to assess for the presence of AKI.

Once potentially eligible participants are identified:

- Research personnel will enroll subjects into the study and a copy of the informed consent will be provided.
- Participants will be given one week to consider the study before requesting the return of the informed consent.
    - As critically ill patients are often temporarily mentally disabled due to the nature of their underlying illness or receiving sedative medications for their safety and comfort, surrogate consent will be obtained for patients initially if the patient cannot provide informed consent. Patients in whom surrogate is obtained during hospitalization will need to provide informed consent by the three-month visit. Patients unable to provide informed consent by the three-month visit will be ineligible for the longitudinal study.
- If participants are not dialysis-dependent at discharge, continue to meet eligibility criteria, and agree to participate in the study, participants will be invited to attend the three-month study visit where informed consent will be obtained for long-term follow up.

1.55.3 Kaiser Permanente Northern California

Kaiser will recruit 157 adult AKI participants and 157 adult matched non-AKI participants from up to three Kaiser medical centers as described below:

For AKI participants:

- Research personnel will go to each recruiting hospital and after confirming access to the AKI participant, obtain written consent from the participant to complete a short questionnaire, to obtain a single non-fasting blood specimen and random urine sample, and to confirm the participant's agreement to be contacted within the next 30 days to discuss the study further.
- Within 30 to 45 days after hospitalization, a follow-up letter from the CRC PI will be sent to each AKI participant enrolled during the acute hospitalization to introduce the long-term study protocol.
- One week after sending the letter, research personnel will call the AKI participant to screen for remaining eligibility and to schedule the three-month visit.
- At the three-month visit (conducted at a central research clinic in Oakland), research personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.
- Research personnel also will review the consent at the 12-month follow-up visit to reinforce the schedule and study protocol with the participant.

For non-AKI participants:

- After an AKI participant successfully completes a three-month study visit, research personnel will identify a pool of up to ten possible matched non-AKI participants who are hospitalized within a recent time frame of the enrolled AKI participant.
- Prior to hospital discharge, research personnel will go to each recruiting hospital and after confirming access to the potential non-AKI participant, obtain written consent from the non-AKI participant to complete a short questionnaire, to obtain a single non-fasting blood specimen and random urine sample, and to confirm the participant's agreement to be contacted within the next 30 days to discuss the study further.
- Within 30 to 45 days after hospitalization, a follow-up letter from the CRC PI will be sent to each non-AKI participant enrolled during the acute hospitalization to introduce the long-term study protocol.
- One week after sending the letter, research personnel will call the non-AKI participant to screen for remaining eligibility and to schedule the three-month visit.
- At the three-month visit, research personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.
- Research personnel also will review the consent at the 12-month follow-up visit to reinforce the schedule and study protocol with the participant.

1.55.4 University of Washington

The University of Washington will recruit 200 adult AKI participants and 200 matched adult non-AKI participants from the ICU's at Harborview Medical Center. Patients in the trauma, surgical, and medical ICU's will be screened daily for inclusion/exclusion criteria. We will seek IRB permission to initiate collection of samples before consent has been obtained. This will allow us to enroll patients who are too ill to provide consent but are without local surrogates. If consent is not obtained, these samples will be destroyed.

Patients/surrogates will be approached for possible consent into the ASSESS-AKI study on day 1 of their hospitalization. Upon this initial contact, we will ask for consent for participation in a short questionnaire, collection of study samples, and permission for further contact for long term aspects of the study. We will obtain additional contact names/numbers as well. We anticipate two possible scenarios for the consent process of study subjects.

Cohort 1:

1) For those patients with a pre-hospitalization creatinine within the past 365 days documented in the medical record, immediate enrollment into the study can occur. Sample collection will be initiated and serum creatinine data will be extracted from the electronic medical record to assess for the presence of AKI.
2) Patients in whom surrogate consent is obtained during hospitalization will need to provide informed consent by the three-month visit and efforts will be made to obtain consent before hospital discharge. Patients unable to provide informed consent by the three month visit will be ineligible for the longitudinal study.

3) We anticipate that given the proposed matched parallel cohort design, we will be enrolling both AKI participants (those who experience AKI) and non-AKI participants (those who do not suffer an AKI episode) and will ultimately be matched on a minimal set of key confounding characteristics per study protocol.

Cohort 2:

1) For patients without a pre-hospitalization creatinine, we will ask for consent as noted above, and will additionally ask for signatures on a Release of Medical Information form so that primary care or referral providers may be contacted for potential creatinine values within the past year. If obtained, verification that creatinine values were obtained from IDMS-standardized laboratories will occur. Sample collection will be initiated. If creatinine values are unable to be determined, these subjects will not be contacted for the follow up portion of the study.
2) If surrogate consent has been obtained, subjects will be re-consented before discharge and concurrently approached for consent to place their samples and data in the University of Washington KRI Data and Biosample Repository.

Within 1-3 weeks following discharge, materials will be mailed to all potential AKI and non-AKI participants enrolled during the acute hospitalization to introduce the long term follow up protocol. Two additional strategies include the following: (1) a thank you letter and pamphlet with study name, logo, and information including contact numbers and photos of investigators and coordinators will be sent post discharge; (2) we will offer to coordinate research visits with return physician visit appointments if patient prefers, we will offer parking validation, and also the choice for the visit to take place in the participants' homes for their convenience One week after mailing, research personnel will call eligible participants to answer potential questions, screen for remaining eligibility, and invite them to attend the three-month study visit.

At the three-month visit (conducted at the University of Washington KRI facilities and laboratory or in patient home), research personnel will obtain written consent for participation in the long-term study and conduct the three-month visit protocol on the same day.

1.54.5 Gender and Racial/Ethnic Representation

ASSESS-AKI will target recruitment of a study sample with a broad gender and racial/ethnic diversity that is representative of the AKI population in the U.S.

1.54.6 Recruitment Period

The ASSESS-AKI 24-month Recruitment Period has been projected to run from December 2009 to December 2012 for the Kaiser and Yale sites and December 2009 to February 2015 for the Vanderbilt site. The recruitment period for the University of Washington is projected to run from January 2011 to February 2015.

1.56 REENROLLMENT

Pediatric participants, who do not qualify for enrollment at or prior to Visit 3M for reasons that may be overcome with time, may be allowed to re-enter the study for a second try. For example, a parent may not consent for a child that is two months old but if the child returns for cardiac surgery at one-year of age, the parent may consider enrollment. Only participants, who have a high probability of success on the second try, should be afforded this option.

If a participant re-enters the study, he/she must be given a new Participant ID number from the Participant Assignment Log (CASE/CTRL_PART_ASSIGN).

- New copies of the ASSESS-AKI informed consent and participant assent documents must be read and signed. The documents signed at the initial enrollment should reside in the folder created for the participant's original participant ID number. The new signed consent and assent documents should reside in the participant's current study folder. The informed consent and participant assent should not be updated with initials and the date, as this practice violates institutional procedures at some of the clinical sites.
- The following form may be reused from the original Visit 0: Participant Contact (P2_CONTACT). This form should be reviewed and updated, as necessary, with the participant/parent/guardian upon re-entry. The forms must also be updated with the new Participant ID and Visit 0 date and initialed by the Research Coordinator. Copies should be placed in both the old and new participant study folders.

All other procedures, labs, and blood and urine samples must be repeated for each reenrolled pediatric participant in ASSESS-AKI. Once enrolled at Visit 3M for the outpatient phase, the pediatric participant is not eligible to re-enter the inpatient period.

1.57 REPEATING AN OUTPATIENT VISIT

The full visit may be repeated within the visit window, which is+/- four weeks from the ideal visit date for Visit 3M and +/- six weeks from the ideal visit date for the subsequent outpatient in-person visits. Urine and blood samples must be collected within the 48-hour window of the visit date. All forms must be reviewed for accuracy with the participants with the exception of the background and personal information that has not changed.

If the samples cannot be collected within the 48-hour window of the first incomplete visit, any collected biomarkers will be destroyed. This is true for ECG, blood, and urine.

1.58 SCREEN FAILURE

Sites will only report on the people who were eligible and approached rather than on every person eligible. If a participant becomes ineligible prior to or at the three-month visit, it is a screen failure.

1.59 SF-12v2™ Health Survey (SF-12v2™)

The SF-12v2™ Health Survey (SF-12v2™) is self-administered to the adult participants during the outpatient, in-person visits. This form is not completed by the pediatric participants. This form takes about two minutes to complete and is written at an eighth grade reading level.

The survey was developed as an alternative to the SF-36 for use in large surveys of general and specific populations as well as larger longitudinal studies of health outcomes. It is a 12-item subset of the SF-36v2™ that measures the same eight domains of health and is intended to be a brief, reliable measure of overall health status.

Question 1:	General Health
Question 2a, 2b:	Physical Functioning
Question 3a, 3b:	Role Physical
Question 4a, 4b:	Role Emotional
Question 5:	Bodily Pain
Question 6a, 6c:	Mental Health
Question 6b:	Vitality
Question 7:	Social Functioning

The License Agreement is between Penn State University and Quality Metric; License Number CT120084/OP003499. The License term is March 25, 2012 to March 24, 2016. The Principal Investigator at each clinical research site, who is administering the SF-12v2™, must complete an Acknowledgement by Agent, which is forwarded to the DCC and Quality Metric.

1.60 SOCIAL SECURITY NUMBER

A YES/NO question about providing a social security number is in the informed consent with a signature requirement. If participants are not comfortable about providing their social security numbers, explain to them how the number will be used and stored. The social security number is optional.

The social security number will be used to connect with other medical databases, such as Medicare, and to ascertain Social Security vital status files among participants who are lost to follow-up. The Canadian Yale sites will not be obtaining a healthcare number. The numbers will be stored in a secure location separate from the participant chart and will not be sent to the DCC. Kaiser Permanente will store the social security numbers in a scrambled fashion.

1.61 STUDY CYCLE

The ASSESS-AKI study is funded for ten years for Kaiser, Vanderbilt, and Yale sites (September 1, 2008 to June 30, 2018) and five years for the University of Washington (September 2010 to September 2015). The first year focused on protocol development, forms development, contracts with an ECG reading center (Wake Forest) and a central laboratory (University of Minnesota), and staff training. The recruitment phase began in the second year and participants are followed for a minimum of four years. The Recruitment Period has been projected to run from December 2009 to March 2013 for the Yale sites, December 2009 to June 2013 for the Kaiser site, December 2009 to February 2015 for the Vanderbilt site, and from January 2011 to February 2015 for the University of Washington. The final months of the project will focus on evaluation and data analysis for publication and presentation.

1.62 STUDY ORGANIZATION

1.62.1 Clinical Research Centers (CRC) and Sites

CRC	PRINCIPAL INVESTIGATOR	LOCATION
Kaiser Permanente Northern California	Alan S. Go, MD	Oakland, CA
Vanderbilt University	Talat Alp Ikizler, MD	Nashville, TN
Yale University London Health Sciences Center Montreal Children's Hospital Univ. of Cincinnati Children's Hospital Yale University	Chirag Parikh, MD, PhD	New Haven, CT
University of Washington	Jonathan Himmelfarb, MD	Seattle, WA

1.62.2 Data Coordinating Center

The Pennsylvania State University
Department of Public Health Sciences
Hershey, PA

Principal Investigator:	Vernon M. Chinchilli, PhD
Co-Investigators:	Nasrollah Ghahramani, MD, MS
	W. Brian Reeves, MD
	Jennifer Schaub, MD
	Lan Kong, PhD
	Ming Wang, PhD

1.62.3 Funding

Funding for ASSESS-AKI is provided by the National Institute of Diabetes, Digestive and Kidney diseases (NIDDK), a division of the National Institutes of Health (NIH), Department of Health and Human Services.

1.62.4 NIDDK

Robert A. Star, MD
Paul L. Kimmel, MD
Kevin Abbott, MD, MPH
Yining Xie, PhD

1.62.5 Steering Committee Chair

James Kaufman, MD

1.62.6 External Expert Panel (EEP)

Thomas Hostetter, MD (Chair)
Myra Carpenter, PhD
Charles Herzog, MD
Stephen Hewitt, MD, PhD
Jon Klein, MD, PhD
Michael Pencina, PhD
Stephen Rich, PhD
Aliza Thompson, MD, MS
Taylor Thompson, MD

Refer to Section 2.B.1., Consortium Organization, in the GENERAL MOP.

1.63 TELEPHONE CALLS

The 6-, 18-, 30-, 42-, 54-, 66-, 78-, and 90-month contacts will consist of telephone calls, lasting an estimated 10 to 15 minutes, to collect relevant outcome and medication use data and to update contact information.

1.63.1 Obstacles to reaching potential participants

- Wrong or disconnected numbers
    - If a phone number is wrong or disconnected, indicate this information on the Adult/Pediatric Contact Information (ADULT_CONTACT/PEDS_CONTACT) form.
    - Try to contact this participant again by mail.
- Blocked/fast busy numbers
    - If a blocked number or a fast busy signal is reached, ask the operator to complete the call. The Research Coordinator should tell the operator that he/she is having difficulty with the number. Do not say that the number is blocked. Request that the operator complete the call. If asked, tell the operator to bill the call to the outgoing number.
- When to call
    - If the potential participant cannot be reached, ask if there is a better time to call or another number where they may be reached.
- How many times to call
    - Make several attempts to contact participants. Try each number (day, evening, and weekend) at least twice during each of the following time periods (10:00 AM – Noon, Noon – 6:00 PM, 6:00PM – 8:30 PM, and anytime during the weekend) before leaving a message. If there is still no answer, leave a message such as the following:

      Hello, my name is [NAME]. I'm calling on behalf of [CENTER/SITE NAME] about an inquiry (he/she or you) made at our medical center. We would like to speak with [NAME OF PARTICIPANT]. Would you please call our toll-free number at NNN-NNN-NNNN and leave your name, your phone number with area code, and a good time to reach you? Thank you very much.
    - Do not leave more than one message every couple of days. Do not leave repeated messages. Use your best judgment if calls are being avoided or simply bad timing. If the participant cannot be reached, file this information and plan to call again in a few weeks or contact the participant by mail.
    - Document the missed calls in the participant's folder.

1.63.2 Participants Who Relocate

See PARTICIPANTS WHO RELOCATE in the PROTOCL SPECIFIC MOP.

1.64 TIME ZERO

For AKI participants, Time Zero is the date of the detected AKI episode that prompted initial enrollment which includes obtaining at least one set of blood and urine specimens up to 96 hours after the AKI episode.

For non-AKI participants, Time Zero is the date of hospital discharge. These participants will not have any relevant event during the index hospitalization to anchor to because they will likely have relatively short hospital lengths of stay.

1.65 TRAILS B

Trails B is to be administered to each adult at the 3-, 12-, 24-, and 36-month, in-person visits and if applicable, prior to the Modified Mini-Mental State Exam (3MS). It offers an assessment of cognitive function with the sensitivity for detecting cognitive dysfunction and it is brief. TRAILS A is not administered. Coordinators must be certified to administer the TRAILS B. Certification began on June 18, 2010.

The Reasons for Missing TRAILS B spreadsheets can be found on the ASSESS website, and the coordinator has access only to its site's spreadsheet. Refer to the Document Management MOP, Section 2 for more information on how to fill out the spreadsheet. There are also instructions in the Reasons for Missing TRAILS B folder under "How to Fill Out Missing TRAILS B Sheet."

1.65.1 TRAILSB_SCORE

TRAILSB_SCORE, Q1000: The range is 0-22 years and the completion of GED equals 12 years.

TRAILSB_SCORE, Q1010: The range is 0-300 seconds. Five minutes equals 300 seconds. If the participant has not completed the task after five minutes, stop the task and enter 999.

Refer to the Quality of Life/Cognitive Function Manual for administering and scoring the test.

1.66 URINALYSIS

After December 14, 2011, microscopy is not mandatory for ASSESS participants. Standard urinalysis on an in-hospital urine sample from non-AKI and AKI participants is performed by the coordinators utilizing the Bayer Clinitek. For AKI participants, the urine sample is collected anytime within 96 hours at or after the AKI occurrence. For non-AKI participants, the urine sample is collected anytime within 96 hours of enrollment.

The coordinator should contact the DCC for a protocol exception if unable to perform the dipstick.

See 1.63 URINE DIPSTICK in the PROTOCOL SPECIFIC MOP.

Before December 14, 2011, standard urinalysis with microscopy was performed at the local hospital laboratory ONLY on an in-hospital urine sample from non-AKI and AKI participants. For AKI participants, the urine sample is collected anytime within 96 hours at or after the AKI occurrence. For non-AKI participants, the urine sample is collected anytime within 96 hours of enrollment. Microscopy was to be performed at the same time that the urine sample that was collected for biomarkers. Urine microscopy was sent to the local lab, not reviewed by investigators. If no urine microscopy is performed due to a negative (or clean) dip, Q1090 should be answered 'Yes', Q1100-1170 marked as 'less than 5' and Q1180 marked as 'No'. This was mandatory for adult participants and suggested for pediatric participants. Do not send urine to the lab for urinalysis and microscopy if collected by the cotton ball technique. The coordinator should contact the DCC for a protocol exception if unable to perform the urinalysis with microscopy unless this is due to a negative dip.

1.67 URINE DIPSTICK

The Bayer Clinitek Status Analyzer is used by the sites to produce a printout of the urine dipstick results, which are recorded on the Urine Dipstick Results (DIPSTICK) form. The Analyzer is auto-calibrating. For more information, refer to the Equipment Training slides and/or the Bayer Clinitek Status Analyzer User Manual.

The coordinator should consult the site PI for any values outside of the range to determine if additional follow-up is needed.

Dipstick results that are collected within the 48-hour collection window may be data entered. If the full visit is rescheduled, the dipstick would need to be repeated.

The coordinator should contact the DCC for a protocol exception if unable to perform the dipstick.

1.68 URINE SAMPLING PROCEDURES

1.68.1 Inpatient Phase

Anuria is defined as <50cc/day and is not a contraindication to urine collection. If there is not enough urine during the index hospitalization, the coordinator should come back to collect more urine. However, multiple collections should not be pooled; rather, the coordinator should come back and collect urine for a longer period of time to meet the minimum urine volume. If an adult AKI participant is unable to produce at least 3cc of urine within the allowable time period due to severity of AKI, then the recruiter will continue to enroll the participant, only collect blood, and request a protocol exception from the DCC Scientific Coordinator.

1.68.2 Outpatient Phase

If the participant is unable to provide urine, there is a 48-hour window of the study visit for collection of the urine sample of adult and pediatric participants during the outpatient phase. Multiple urine samples should not be pooled. If the urine sample is not collected within the 48-hour window, reschedule the visit to attempt the collection again within the visit window. This window is +/- four weeks of ideal date for Visit 3M and +/- six weeks of ideal date for yearly visits.

See 1.7 BIOMARKER SAMPLE COLLECTION in the PROTOCOL SPECIFIC MOP. Refer to the BIOSPECIMEN MOP.

1.69 VISIT 0

This contact will occur during the hospitalization.

1.69.1 Checklist

Informed consent process

Social security number (SSN)

Registry form (REGISTRY)

Demographics (P1/P2_INPT_DEMO)

Contact Information (P1/P2 _CONTACT)

Eligibility Assessment (ELIG1A)

Inpatient Assessment (P1/P2_INPATIENT1, P1/P2_INPATIENT2)

Baseline serum creatinine (BASE_CREATININE)

Blood Draw and Urine Sample (P1/P2_INPT_SPEC)

Pediatric Inpatient DNA Specimen Collection (P2_INPT_DNA_SPEC) – Pediatric participants only

DNA Consent (DNA_CONSENT) - Pediatric participants only

Urine Dipstick (DIPSTICK)

Inpatient serum creatinine (INPT_CREATININE)

Participant Assignment Log (CASE/CTRL_PART_ASSIGN)

- Potential participants will sign and date a written consent to participate prior to data collection. A copy of the signed informed consent will be given to the participant and the original consent kept in the participant study file.
- Research coordinator (RC) will refer to the Inpatient Visit Procedure Checklist (INPATIENT_CHK).
- Prior to entry of the baseline data, the RC will be required to register the participant in the DMS and enroll the participant in the ASSESS-AKI study (CASE/CTRL_PART_ASSIGN).
- The value of the baseline serum creatinine will need to be recorded to answer Eligibility Assessment (ELIG1A), Q1000/Q1005.
- RC will assess eligibility by interviewing the potential participant and recording the responses on the ELIG1A. The ELIG1A will determine if the potential participant appears eligible or ineligible for the ASSESS-AKI study. Answer all of the questions. Do not stop completing the form if a shaded box is marked.
- If RC and PI are unable to make a decision of eligibility, any further Visit 0 activities should be deferred until a final determination can be made. Contact the DCC.
- RC will collect a sample of blood and urine sample. Fasting is not required prior to providing a blood sample.

  - Adults: Mandatory minimum collection of three 0.5mL aliquots of EDTA plasma and three 1.0mL aliquots of urine. If an adult participant is anuric (i.e., unable to produce the 3mL of urine during the inpatient stay) due to AKI, the participant will not be excluded from the study. The site coordinator should request a protocol exception from the DCC Scientific Coordinator.
  - Pediatrics: No mandatory minimum.
- Pediatrics only: RC collects a DNA sample using the Pediatric Inpatient DNA Specimen Collection (P2_INPT_DNA_SPEC). The specimen is to be held at the site until the Rutgers Biorepository confirms receipt of ACD-A or V12M/V24M could not occur.
- Bayer Clinitek Status Analyzer results are recorded on the Urine Dipstick Results (DIPSTICK) form per the Equipment Training slides.
- Inpatient Assessment (P1/P2_INPATIENT1) should be completed by chart review. The RC should review these forms for completeness prior to ending the visit.
- The RC and the participant will complete the Contact Information (P1/P2_CONTACT) and Demographics (P1/P2_INPT_DEMO) either by interview or self-administration.
- The RC may need to wait until after hospital discharge to complete the Inpatient Assessment (P1/P2_INPATIENT2).

1.70 VISIT 0B

This phone contact is not required and is intended to further assess eligibility to participate in the study and to schedule the three-month visit.

1.70.1 Checklist

Eligibility Assessment (ELIG1B, ELIG1B_SCRIPT)

- Completion of the Eligibility Assessment (ELIG1B) is not required.
- When the participant has been contacted by phone, the Research Coordinator (RC) should read the Eligibility Checklist 1B Script (ELIG1B_SCRIPT).
- If the participant is willing and available to continue, complete the ELIG1B with the participant.
- If the participant is willing but unable to continue, ask permission to call back and a good time to call.
- If the participant is unwilling to continue, thank the participant for his/her time and provide your toll-free number if s/he would like to participate in the future. Complete the Withdrawal (WITHDR) form.
- If the participant has died, thank the person for his/her time. Complete the Death Record Evaluation (DEATH_EVAL) and Withdrawal (WITHDR) forms.
- If the participant is eligible, schedule the three-month visit.
- Instruct the participant to bring all of his/her recent (within the last 30 days) prescription and over-the-counter medications which he/she takes daily or regularly so they can be identified for collection on the concomitant medication information forms (CMED, CMED_OTC) at the three-month visit.
- If the participant is no longer eligible, explain what has made him/her ineligible and why and thank him/her for his/her time.
- If the participant asks a question and the RC does not know the answer, s/he should offer to find out the information and respond as soon as possible

1.71 VISIT THREE-MONTH (3M)

This is the first in-person visit of the outpatient phase of the ASSESS-AKI study. Eligibility is further assessed prior to entering the outpatient phase and matching.

1.71.1 Checklist

Eligibility Assessment (ELIG2)

Outpatient Demographics (P1/P2_OUTPT_DEMO)

Medical History (P1/P2_MEDHX)

Medical Events (P1/P2_EVENTS, HOSP_EVAL, ICD9_CPT_CODES or ICD10_CCI_CODES, INPT_CREATININE, DEATH_EVAL)

Lifestyle assessment (P1/P2_LIFESTYLE_3M)

Quality of Life assessment (SF-12, PedQL, TRAILS B, TRAILSB_SCORE, MMMSE, MMMSE_TALLY, MMMSE_TALLY_PC)

Short Physical Exam (BLOOD_PRESSURE, SEXAM)

Urine Dipstick (DIPSTICK)

ECG Clinic (ECG_CLINIC) – adult sites only

Alert values (P1/P2_ALERT)

Update contact information (P1/P2_CONTACT)

Concomitant Medications (CMED, CMED_OTC)

Laboratory Results CBC (CAN_LABCBC, US_LABCBC) – Adult participants only

Outpatient V3M Specimen Collection and Processing (P1/P2_V3M_COLLECT_BLD, P1/P2_V3M_COLLECT_BLD_2, P1/P2_V3M_COLLECT_UA, P1/P2_V3M_COLLECT_UA_2, P1/P2_V3M_PROCESS, P1/P2_V3M_PROCESS_2)

DNA Collection (DNA_DBGAP_CONSENT) – Adult participant only

- Visit 3M must occur within three months of Time Zero with a window of ±four (4) weeks.
- Fasting is not required for the blood draw.
- Instruct the participant to bring all of his/her recent (within the last 30 days) prescription medications and over-the-counter medications taken regularly so they can be identified for collection on the concomitant medication form.
- If the participant forgets to bring his/her medications, the Research Coordinator (RC) may collect this information through participant interview. A follow-up phone call to the participant may be necessary to confirm the accuracy of the interview results.
- Eligibility Assessment (ELIG2) is to further assess eligibility before the participant is matched and enrolled in the outpatient phase of the study.
- BP is measured per the Equipment Training Slides. The RC will record the pulse and three sequential blood pressure measurements while the participant is seated.

- Height and weight is measured following the Equipment Training Slides. Height and weight are measured standing. If the participant is unable to stand, record participant's self-report. Record values on SEXAM form.
- Bayer Clinitek Status Analyzer results are recorded on the Urine Dipstick Results (DIPSTICK) form per the Equipment Training slides.
- One 3mL EDTA (purple top) vacutainer for is sent to the local laboratory.
- Adult participants only - RC collects a DNA sample. This is not required in order to be in the study. Use the DNA-dbGAP consent (DNA_DBGAP_CONSENT) form to confirm consent to genetic sample prior to DNA collection. If a DNA sample cannot be collected, attempt to collect DNA at Visit 12M.
- RC collects the blood and urine samples using the Outpatient V3M Specimen Collection (P1/P2_V3M_COLLECT_BLD, P1/P2_V3M_COLLECT_UA) forms and site specific checklist to record reasons not collected.
  - Adults: Mandatory minimum collection of 10mL of whole blood and 20mL of urine
  - Pediatrics: Mandatory minimum collection of 1.6mL of urine for diaper wearers and 5mL of urine for non-diaper wearers; no mandatory minimum of blood
- There is a 48-hour collection window for blood and urine samples.
- The full visit may be repeated within the visit window (+/- four (4) weeks of the ideal date) if the previous collection was not successful. See REPEATING AN OUTPATIENT VISIT in the PROTOCOL SPECIFIC MOP.
- Use Outpatient V3M Specimen Collection 2+ (P1/P2_V3M_COLLECT_BLD_2, P1/P2_V3M_COLLECT_UA_2) forms if you need to attempt the collection within the 48-hour collection window and/or within the visit window.
- The urine and blood samples are processed using the Outpatient V3M Specimen Processing (P1/P2_V3M_PROCESS) form and site specific checklist to record reasons not collected. Use Outpatient V3M Specimen Processing 2+ (P1/P2_V3M_PROCESS_2) form if you needed to collect the samples within the 48-hour collection window and/or within the visit window.
- Review the Contact Information (P1/2_CONTACT) and update if necessary.
- Confirm date and time of six-month phone call (Visit 6M) and 12-month in-person visit (Visit 12M).
- Administer the Quality of Life assessments for adult participants. Short Form 12 (SF-12) and TRAILS B should be administered prior to the MMMSE. Use the TRAILSB_SCORE form to record number of years of education and number of seconds to complete the test. MMMSE interview and phone versions are available. If it is absolutely necessary to end the visit prior to the administration of the MMMSE, the phone version of the MMMSE may be used. Use the appropriate tally sheet.
- Administer the Quality of Life assessments for pediatric participants. The Pediatric QOL inventory (PedsQL) varies among four age groups and may have an accompanying parent questionnaire. RC should confirm the appropriate version prior to administering.
- RC should review forms for completeness prior to ending the visit.
- Adult participants will have an ECG performed according to the electrocardiography Assessment Manual. ECG is not required for pediatric participants. ECG will be read by the ASSESS-AKI central reading center, EPICARE (Wake Forest).

1.72 VISITS 12-MONTH (12M), 36-MONTH (36M)

These are in-person visits that occur one year, and three years after the AKI episode for the AKI participant and after discharge of the index hospitalization for the Non-AKI participant of the outpatient phase of the ASSESS-AKI study.

1.72.1 Checklist

Medical History (P1/P2_MEDHX)

Medical Events (P1/P2_EVENTS, HOSP_EVAL, ICD9_CPT_CODES or ICD10_CCI_CODES, INPT_CREATININE, DEATH_EVAL)

Lifestyle assessment (P1/P2_LIFESTYLE)

Quality of Life assessment (SF-12, PedsQL, TRAILS B, TRAILSB_SCORE, MMMSE, MMMSE_TALLY, MMMSE_TALLY_PC)

Short Physical Exam (BLOOD_PRESSURE, SEXAM)

Urine Dipstick (DIPSTICK)

ECG Clinic (ECG_CLINIC) –adult sites only

Alert values (P1/P2_ALERT)

Update contact information (P1/P2_CONTACT)

Concomitant Medications (CMED, CMED_OTC)

Laboratory Results CBC (CAN_LABCBC, US_LABCBC) – Adult participants only

Outpatient Yearly Specimen Collection and Processing (P1/P2_ OUTPT _COLLECT_BLD, P2_V12M_COLLECT_BLD, P1/P2_ OUTPT _COLLECT_BLD_2, P1/P2_OUTPT_COLLECT_UA, P2_V12M_COLLECT_UA, P1/P2_OUTPT_COLLECT_UA_2, P1/P2_ OUTPT _PROCESS, P2_V12M_PROCESS, P1_ OUTPT _PROCESS_2)

DNA Consent (DNA_CONSENT) - Pediatric participants only at V12M

If not collected at Visit 3M, DNA Collection (DNA_DBGAP_CONSENT) at Visit 12M only – Adult participants only. If re-consenting at Kaiser site, confirm consent on DNA_CONSENT form and answer Q995 and Q1040 on DNA_DBGAP_CONSENT form.

- RC may refer to the OUTPT_VISIT_CHK1 for Visit 12M and Visit 36M.
- Visit 12M must occur within six months of Visit 6M with a window of ±six (6) weeks. Visit 36M must occur within six (6) months of Visit 30M with a window of ±six (6) weeks.
- Fasting is not required for the blood draw.
- Instruct the participant to bring all of his/her recent (within the last 30 days) prescription medications and over-the-counter medications taken regularly so they can be identified for collection on the concomitant medication form.
- If the participant forgets to bring his/her medications, the RC may collect this information through participant interview. A follow-up phone call to the participant may be necessary to confirm the accuracy of the interview results.

- BP is measured per the Equipment Training Slides. The RC will record the pulse and three sequential blood pressure measurements while the participant is seated.
- Height and weight is measured following the Equipment Training Slides. Height and weight are measured standing. If the participant is unable to stand, record participant's self-report. Record values on Short Physical Exam (SEXAM) form.
- Bayer Clintek Status Analyzer results are recorded on the Urine Dipstick Results (DIPSTICK) form per the Equipment Training slides.
- One 3mL EDTA (purple top) vacutainer for CBC is sent to the local laboratory.
- Adult participants only - RC collects a DNA sample at V12M, only if not collected at V3M. This is not required in order to be in the study. Use the DNA consent (DNA_DBGAP_CONSENT) form to confirm consent to genetic sample prior to DNA collection. If re-consenting at Kaiser site, confirm consent on DNA_CONSENT form and answer Q995 and Q1040 on DNA_DBGAP_CONSENT form.
- Pediatric participants only - RC collects a DNA sample. This is not required in order to be in the study. Use the DNA consent (DNA_CONSENT) form to confirm consent to genetic sample prior to DNA collection. If a DNA sample cannot be collected, attempt to collect DNA at Visit 24M.
- Adult participants only - RC collects the blood and urine samples using the Outpatient Yearly Specimen Collection (P1_OUTPT _COLLECT_BLD, P1_ OUTPT _COLLECT_UA) forms and site specific checklist to record reasons not collected.
- Pediatric participants only - RC collects the blood and urine samples using the either the Outpatient V12M Specimen Collection (P2_V12M_COLLECT_BLD, P2_ V12M_COLLECT_UA) or the Outpatient Yearly Specimen Collection (P2_OUTPT _COLLECT_BLD, P2_ OUTPT _COLLECT_UA) forms and site specific checklist to record reasons not collected.
    - Pediatrics at V12M: Mandatory minimum of 0.175 mL of plasma and 1.6mL of urine for diaper-wearers and 5mL for non-diaper wearers.
- There is a 48-hour collection window for blood and urine samples.
- The full visit may be repeated within the visit window (+/- six (6) weeks of the ideal date) if the previous collection was not successful. See REPEATING AN OUTPATIENT VISIT in the PROTOCOL SPECIFIC MOP.
- Adult participants only - Use Outpatient Yearly Specimen Collection 2+ (P1_OUTPT_COLLECT_BLD_2, P1_ OUTPT_COLLECT_UA_2) forms if you need to attempt the collection within the 48-hour collection window and/or within the visit window.
- Pediatric participants only - Use either the Outpatient V12M Specimen Collection 2+ (P2_V12M_COLLECT_BLD_2, P2_V12M_COLLECT_UA_2) or Outpatient Yearly Specimen Collection 2+ (P2_OUTPT_COLLECT_BLD_2, P2_ OUTPT_COLLECT_UA_2) forms if you need to attempt the collection within the 48-hour collection window and/or within the visit window.
- Adult participants only - The urine and blood samples are processed using the Outpatient Yearly Specimen Processing (P1_ OUTPT_PROCESS) form and site specific checklist to record reasons not collected. Use Outpatient Yearly Specimen Processing 2+ (P1_ OUTPT_PROCESS_2) form if you needed to collect the samples within the 48-hour collection window and/or within the visit window.

- Pediatric participants only - The urine and blood samples are processed using either the Outpatient V12M Specimen Processing (P2_ V12M_PROCESS) or Outpatient Yearly Specimen Processing (P2_ OUTPT_PROCESS) form and site specific checklist to record reasons not collected. Use either the Outpatient V12M Specimen Processing 2+ (P2_ V12M_PROCESS_2) or Outpatient Yearly Specimen Processing 2+ (P2_ OUTPT_PROCESS_2) forms if you needed to collect the samples within the 48-hour collection window and/or within the visit window.
- Review the Contact Information (P1/P2_CONTACT) and update if necessary.
- Administer the Quality of Life assessments. Short Form 12 (SF-12) and TRAILS B should be administered prior to the MMMSE. TRAILS B and MMMSE are administered at V12M and V36M.- Use the TRAILSB_SCORE form to record number of years of education and number of seconds to complete the test. MMMSE interview and phone versions are available. If it is absolutely necessary to end the visit prior to the administration of the MMMSE, the phone version of the MMMSE may be used. Use the appropriate tally sheet. The Pediatric QOL inventory (PedsQL) varies among four age groups and may have an accompanying parent questionnaire. RC should confirm the appropriate version prior to administering.
- RC should review forms for completeness prior to ending the visit.
- Adult participants will have an ECG performed according to the electrocardiography Assessment Manual. ECG is not required for pediatric participants. ECG will be read by the ASSESS-AKI central reading center, EPICARE (Wake Forest).
- At Visit 12M, confirm date and time of 18-month phone call (Visit 18M) and 24-month in-person visit (Visit 24M).
- At Visit 36M, confirm date and time of 42-month phone call (Visit 42M) and 48-month in-person visit (Visit 48M).

1.73 VISITS 24-MONTH (24M), 48-MONTH (48M)

These are in-person visits that occur two years and four years after the AKI episode for the AKI participant and after discharge of the index hospitalization for the Non-AKI participant of the outpatient phase of the ASSESS-AKI study.

1.73.1 Checklist

Medical History (P1/P2_MEDHX)

Medical Events (P1/P2_EVENTS, HOSP_EVAL, ICD9_CPT_CODES or ICD10_CCI_CODES, INPT_CREATININE, DEATH_EVAL)

Lifestyle assessment (P1/P2_LIFESTYLE)

Quality of Life assessment (SF-12, PedsQL, TRAILS B, TRAILSB_SCORE)

Short Physical Exam (BLOOD_PRESSURE, SEXAM)

Urine Dipstick (DIPSTICK)

ECG Clinic (ECG_CLINIC) - adult sites only

Alert values (P1/P2_ALERT)

Update contact information (P1/P2_CONTACT)

Concomitant Medications (CMED, CMED_OTC)

Laboratory Results CBC (CAN_LABCBC, US_LABCBC) – Adult participants only

Outpatient Yearly Specimen Collection and Processing (P1/P2_ OUTPT _COLLECT_BLD, P1/P2_ OUTPT _COLLECT_BLD_2, P1/P2_OUTPT_COLLECT_UA, P1/P2_OUTPT_COLLECT_UA_2, P1/P2_ OUTPT _PROCESS, P1/P2_ OUTPT _PROCESS_2)

If DNA is not collected at V12M, DNA Consent (DNA_CONSENT) - Pediatric participants only at V24M

- RC may refer to the OUTPT_VISIT_CHK2 for Visit 24M and for Visit 48M.
- Visit 24M must occur within six (6) months of Visit 18M with a window of ± six (6) weeks. Visit 48M must occur within six (6) months of Visit 42M with a window of ± six (6) weeks.
- Fasting is not required for the blood draw.
- Instruct the participant to bring all of his/her recent (within the last 30 days) prescription medications and over-the-counter medications taken regularly so they can be identified for collection on the concomitant medication form.
- If the participant forgets to bring his/her medications, the RC may collect this information through participant interview. A follow-up phone call to the participant may be necessary to confirm the accuracy of the interview results.
- BP is measured per the Equipment Training Slides. The RC will record the pulse and three sequential blood pressure measurements while the participant is seated.
- Height and weight is measured following the Equipment Training Slides. Height and weight are measured standing. If the participant is unable to stand, record participant's self-report. Record values on Short Physical Exam (SEXAM) form.

- Bayer Clintek Status Analyzer results are recorded on the Urine Dipstick Results (DIPSTICK) form per the Equipment Training slides.
- One 3mL EDTA (purple top) vacutainer for CBC is sent to the local laboratory.
- RC collects the blood and urine samples using the Outpatient Yearly Specimen Collection (P1/P2_OUTPT _COLLECT_BLD, P1/P2_ OUTPT _COLLECT_UA) forms and site specific checklist to record reasons not collected.
- There is a 48-hour collection window for blood and urine samples.
- The full visit may be repeated within the visit window (+/- six (6) weeks of the ideal date) if the previous collection was not successful. See REPEATING AN OUTPATIENT VISIT in the PROTOCOL SPECIFIC MOP.
- The urine and blood samples are processed using the Outpatient Yearly Specimen Processing (P1/P2_ OUTPT _PROCESS) form and site specific checklist to record reasons not collected.
- Use the Outpatient Yearly Specimen Collection 2+ (P1/P2_OUTPT_COLLECT_BLD_2, P1/P2_ OUTPT_COLLECT_UA_2) forms if you need to attempt the collection within the 48-hour collection window and/or within the visit window.
- The urine and blood samples are processed using the Outpatient Yearly Specimen Processing (P1/P2_ OUTPT_PROCESS) form and site specific checklist to record reasons not collected. Use Outpatient Yearly Specimen Processing 2+ (P1/P2_ OUTPT_PROCESS_2) form if you needed to collect the samples within the 48-hour collection window and/or within the visit window.
- Pediatric participants only - If not collected at V12M, RC collects a DNA sample and DNA Consent (DNA_CONSENT)
- Review the P1/P2_CONTACT form and update if necessary.
- Administer the Quality of Life assessments, Short Form 12 (SF-12) and TRAILS B. TRAILS B is administered at V24M only. Use the TRAILSB_SCORE form to record number of years of education and number of seconds to complete the test. The Pediatric QOL inventory (PedsQL) varies among four age groups and may have an accompanying parent questionnaire. RC should confirm the appropriate version prior to administering.
- RC should review forms for completeness prior to ending the visit.
- Adult participants will have an ECG performed according to the electrocardiography Assessment Manual. ECG is not required for pediatric participants. ECG will be read by the ASSESS-AKI central reading center, EPICARE (Wake Forest).
- At Visit 24M, confirm date and time of 30-month phone call (Visit 30M) and 36-month in-person visit (Visit 36M).
- At Visit 48M, confirm date and time of 54-month phone call (Visit 54M) and 60-month in-person visit (Visit 60M).

1.74 VISITS 60-MONTH (60M), 72-MONTH (72M), and 84-MONTH (84M)

These are in-person visits that occur five years, six years, seven years, and eight years after the AKI episode for the AKI participant and after discharge of the index hospitalization for the Non-AKI participant of the outpatient phase of the ASSESS-AKI study.

1.74.1 Checklist

Medical History (P1/P2_MEDHX)

Medical Events (P1/P2_EVENTS, HOSP_EVAL, ICD9_CPT_CODES or ICD10_CCI_CODES, INPT_CREATININE, DEATH_EVAL)

Lifestyle assessment (P1/P2_LIFESTYLE)

Quality of Life assessment (SF-12, PedsQL)

Short Physical Exam (BLOOD_PRESSURE, SEXAM)

Urine Dipstick (DIPSTICK)

ECG Clinic (ECG_CLINIC) - adult sites only

Alert values (P1/P2_ALERT)

Update contact information (P1/P2_CONTACT)

Concomitant Medications (CMED, CMED_OTC)

Laboratory Results CBC (CAN_LABCBC, US_LABCBC) – Adult participants only

Outpatient Yearly Specimen Collection and Processing (P1/P2_ OUTPT _COLLECT_BLD, P1/P2_ OUTPT _COLLECT_BLD_2, P1/P2_OUTPT_COLLECT_UA, P1/P2_OUTPT_COLLECT_UA_2, P1/P2_ OUTPT _PROCESS, P1/P2_ OUTPT _PROCESS_2)

If DNA is not collected at V12M, DNA Consent (DNA_CONSENT) - Pediatric participants only at V24M

- RC may refer to the OUTPT_VISIT_CHK5 for Visit 60M, and 72M.
- Visit 60M must occur within six months of Visit 54M with a window of ±six (6) weeks. Visit 72M must occur within six (6) months of Visit 66M with a window of ± six (6) weeks. Visit 84M must occur within six (6) months of Visit 78M with a window of ±six (6) weeks.
- Fasting is not required for the blood draw.
- Instruct the participant to bring all of his/her recent (within the last 30 days) prescription medications and over-the-counter medications taken regularly so they can be identified for collection on the concomitant medication form.
- If the participant forgets to bring his/her medications, the RC may collect this information through participant interview. A follow-up phone call to the participant may be necessary to confirm the accuracy of the interview results.
- BP is measured per the Equipment Training Slides. The RC will record the pulse and three sequential blood pressure measurements while the participant is seated.

- Height and weight is measured following the Equipment Training Slides. Height and weight are measured standing. If the participant is unable to stand, record participant's self-report. Record values on Short Physical Exam (SEXAM) form.
- Bayer Clintek Status Analyzer results are recorded on the Urine Dipstick Results (DIPSTICK) form per the Equipment Training slides.
- One 3mL EDTA (purple top) vacutainer for CBC is sent to the local laboratory.
- RC collects the blood and urine samples using the Outpatient Yearly Specimen Collection (P1/P2_OUTPT _COLLECT_BLD, P1/P2_ OUTPT _COLLECT_UA) forms and site specific checklist to record reasons not collected.
- There is a 48-hour collection window for blood and urine samples.
- The full visit may be repeated within the visit window (+/- six (6) weeks of the ideal date) if the previous collection was not successful. See REPEATING AN OUTPATIENT VISIT in the PROTOCOL SPECIFIC MOP.
- The urine and blood samples are processed using the Outpatient Yearly Specimen Processing (P1/P2_ OUTPT _PROCESS) form and site specific checklist to record reasons not collected.
- Use the Outpatient Yearly Specimen Collection 2+ (P1/P2_OUTPT_COLLECT_BLD_2, P1/P2_ OUTPT_COLLECT_UA_2) forms if you need to attempt the collection within the 48-hour collection window and/or within the visit window.
- The urine and blood samples are processed using the Outpatient Yearly Specimen Processing (P1/P2_ OUTPT_PROCESS) form and site specific checklist to record reasons not collected. Use Outpatient Yearly Specimen Processing 2+ (P1/P2_ OUTPT_PROCESS_2) form if you needed to collect the samples within the 48-hour collection window and/or within the visit window.
- Pediatric participants only - If not collected at V12M, RC collects a DNA sample and DNA Consent (DNA_CONSENT)
- Review the P1/P2_CONTACT form and update if necessary.
- Administer the Quality of Life assessments. Short Form 12 (SF-12) is administered to adults. The Pediatric QOL inventory (PedsQL) varies among four age groups and may have an accompanying parent questionnaire. RC should confirm the appropriate version prior to administering.
- RC should review forms for completeness prior to ending the visit.
- Adult participants will have an ECG performed according to the electrocardiography Assessment Manual. ECG is not required for pediatric participants. ECG will be read by the ASSESS-AKI central reading center, EPICARE (Wake Forest).
- At Visit 60M, confirm date and time of 66-month phone call (Visit 66M) and 72-month in-person visit (Visit 72M).
- At Visit 72M, confirm date and time of 78-month phone call (Visit 78M) and 84-month in-person visit (Visit 84M).
- At Visit 84M, confirm date and time of 90-month phone call (Visit 90M).

1.75 WITHDRAWAL AND CLOSEOUT OF STUDY PARTICIPATION

If the participant withdraws from study participation, the Withdrawal form (WITHDR) is used. It is anticipated that over the course of time, a small number of ASSESS-AKI participants may withdraw from the study. Reasons for withdrawal include death of the participant, participants who are lost to follow up, participants who are too ill or no longer wish to participate. This may occur officially by formal written notification from the participants who to a CRC PI, or unofficially when a participant cannot be reached via the usual methods of contact and in whom death cannot be confirmed. Every effort will be made to ensure high rates of long-term retention and to acquire complete data on all participants.

1.75.1 Early Study Withdrawal

The participant (if applicable, parent/guardian) has the right to withdraw consent for study participation at any time and for any reason. The study investigator may also determine by physician discretion that it is in the best interest of the participant to discontinue participation in the trial.

1.75.2 Withdrawals During the Inpatient Phase

If an ASSESS-AKI participant is discovered to be ineligible, the following instructions apply:

Visit 0

- If the informed consent was signed and the participant was deemed ineligible before any Visit 0 data collections forms are completed, there is nothing more to do; Withdrawal (WITHDR) form is not required.
- If the informed consent was signed and any forms (ELIG1A, P1_INPATIENT1, BASE_CREATININE, INPT_CREATININE) completed for the participant, all data collected is entered into the database and you must complete a Withdrawal (WITHDR) form for the participant.

Visit 0B

- Visit 0B is optional but it provides an opportunity to review the eligibility criteria for each participant before he or she starts the long-term phase.
- If the participant was found to be ineligible during Visit 0B, complete and enter the Eligibility Checklist 1B (ELIG1B) and Withdrawal (WITHDR) forms.

In between Visit 0 and Visit 3M

Withdrawal (WITHDR) form is required to be completed and entered into the database. See data entry of V0 forms for participants who do not progress to V3M in the Protocol Specific MOP.

See REENROLLMENT in the PROTOCOL-SPECIFIC MOP for instructions in reenrolling pediatric participants, who are not enrolled into the long-term study.

1.75.3 Withdrawals During the Outpatient Phase

If an ASSESS-AKI participant is discovered to be ineligible, the following instructions apply:

Visit 3M

- If the participant was found to be ineligible during Visit 3M, complete and enter the Eligibility Checklist 2 (ELIG2), Medical Events Questionnaire (P1/P2_EVENTS), Adult/Pediatric Medical History (P1/P2_MEDHX), and Withdrawal (WITHDR) forms.
  - For KAISER AND YALE, since data has not been entered for a participant prior to this visit, all data collected for Visit 0 and the Withdrawal (WITHDR) form will need to be entered into the study database.

Once a participant has been enrolled, all efforts should be made to follow the participant and to collect data on his or her progress for the duration of the study. This even applies to participants who are discovered to be ineligible or who fail to comply with study procedures following enrollment. A Withdrawal (WITHDR) form is completed at the end of the study for each participant.

If an enrolled participant (or his/her parent/guardian) withdraws consent during a visit, any data already collected at that visit should be reported on the data collection forms, entered into the study database, and forwarded to the DCC. A Withdrawal (WITHDR) form should also be submitted.

1.75.4 Participants Who Relocate

See PARTICIPANTS WHO RELOCATE in the PROTOCOL SPECIFIC MOP.

2 DATA COLLECTION AND DATA PROCESSING

2.1 STANDARD DATA COLLECTION FORMS

Standard data collection forms are located on the ASSESS-AKI secure website. The individual forms are posted in alphabetical order by form code, which is located in the lower right-hand corner of each form.

When preparing for a visit, the Research Coordinator will print a complete visit packet from another area on the website; however, this location allows each standard form to be printed individually.

Standard forms are forms created to collect information applicable to both the adult and pediatric participants. Standard forms allow all similar data points to be stored in the same database table.

2.1.1 AKI Evaluation (AKI_EVAL)

Purpose: This form is completed along with the Hospital/ER Visit evaluation for each hospitalization to record the admission date, serum creatinine values, oliguria, and inpatient dialysis treatments that occurred.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M - 48M, as needed for each hospitalization.

Form Instructions:

On March 8, 2012, the QCC deleted the AKI_EVAL as an ASSESS data collection form. The QCC is agreeable with the sites data entering AKI_EVAL for events they've completed entirely. In addition, the QCC is agreeable with all sites not data entering the AKI_EVAL for events they are still in the process of collecting records, reviewing, and/or completing forms for reported events prior to March 8, regardless of the site visit date.

If no qualifying codes are found for AKI during the event adjudication medical record review, the inpatient serum creatinine measures for all events without an AKI code are compared to the participant's most recent study visit serum creatinine from the Central Lab to determine if there is AKI or not.

Question 995. Record the admission date of the hospitalization.

Questions 1000 - 1020. Record the date, value and unit of measure of last outpatient serum creatinine test obtained prior to this hospitalization; this may be the serum creatinine value from the most recent study visit.

Question 1025. N/A may be selected if there was no urine output recorded, or if the recorded output is obviously inaccurate.

Question 1030. If the response is NO, stop completion of the form. If the response is YES, complete Questions 1040 – Q1100.

Question 1040/1050. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Questions 1060-1090. A response must be selected for each modality.

2.1.2 Baseline Serum Creatinine Measures (BASE_CREATININE)

Purpose: This form records all serum creatinine measurements prior to the AKI episode/index hospitalization, which are abstracted from the participant's routine clinical care medical records.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visit 0

Form Instructions:

Complete the Visit Date as the current date the Baseline Serum Creatinine Measures (BASE_CREATININE) form is completed in its entirety (after all values have been collected and recorded).

(FOR KAISER, VANDERBILT, and UNIVERSITY OF WASHINGTON SITES ONLY):
Only serum creatinine values obtained at an IDMS standardized laboratory within 7 to 365 days prior to the index hospitalization will be recorded on this form and entered into the data entry application. If an outside laboratory is using the Siemens/Dade Dimension or NOVA whole blood analyzer, the serum creatinine value may not be used and is not considered to be IDMS calibrated.

(FOR YALE SITES ONLY):
The creatinine results collected for this form will include all values obtained within 365 days prior to surgery. For each participant at Yale sites, the 'baseline' serum creatinine concentration will be considered the pre-op/outpatient/non-emergency test nearest to the index hospitalization within 365 days prior to surgery, excluding newborns of less than one month of age.

Question 1000. Assign a Collection Number to each serum creatinine value obtained from the medical records beginning with the number 01. Each measurement should have a unique collection number. If a measurement is removed after numbering is complete, cross out the information for the row. The collection numbers do not need to be adjusted.

Question 1010. Collection date is a part of the definition of a unique record along with the collection number; therefore a collection will be identified by the collection date and collection number. If there are multiple creatinine values on a given day, record the peak value within the calendar date. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Question 1030. Round the value to the nearest ten hundredths of a decimal. During data entry, remember to enter the decimal place into the field. Example, enter 001.11 instead of just 00111.

Question 1040. The unit mg/dL has been designated as the accepted measurement for the United States sites and umol/L has been designated as the accepted measurement for the Canadian sites.

Questions 1050/1060. During data entry, if the signature is present on the data collection form, enter a '1' into the database. If the signature is missing, leave Q1050 blank. The information in the source documentation box will only be entered for the first record during data entry. This information will auto-populate for each additional record entered.

Question 6000. The comment section for this form will also only be entered once during entry of the first record. The comment for the first record will auto-populate for each additional record that is entered.

Serum creatinines obtained from rehabilitation facilities may be used at the PI's discretion and would need to be documented by the PI in Q6000.

To verify that the values recorded on the form are correct to the best of the sites knowledge, a second individual at the site should review the records. The second individual should sign the form and indicate the date in the shaded source documentation box provided at the bottom of page 1.

The DCC will verify that the BASE_CREATININE form is reviewed within 15 days after V0 for Vanderbilt, Washington, and Yale pediatric sites and 15 days after the V3M visit date for Kaiser and Yale adult sites.

For more specific details pertaining to the baseline serum creatinine, see the Baseline Serum Creatinine

discussion in Section 1.

2.1.3 Blood Pressure (BLOOD_PRESSURE)

Purpose: This form records measured blood pressure and pulse.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Complete the Visit Date as the current date the Blood Pressure (BLOOD_PRESSURE) form is completed.

Note: This date should correspond to the date the measurements were obtained.

The participant should be seated for all blood pressure and pulse measurements.

Question 1000. If this question is answered No, complete Q1010 and STOP completion of the form.

Question 1010. Check the reason why the blood pressure reading could not be completed at this visit. If the question is answered 'equipment failure', please specify what the equipment failure was on the line provided.

Question 1020. Record the time of day that the blood pressure was taken using a 24 hour clock. During data entry, only the numbers should be entered. Do not enter a colon ':' symbol. Example: 1515, not 15:15.

Question 1030. Record the location where the blood pressure measurement was taken. If the question is answered 'Other'. Please specify a response on the line provided.

Question 1040. Each site should label its blood pressure equipment numerically and record the device number used for the measurement.

Questions 1050-1070. Record the arm used, the midpoint circumference of the arm, and the size of the blood pressure cuff used for the blood pressure measurement. Record the midpoint circumference of the arm to the nearest tenth of a centimeter. A tape measure should be used to measure and record the mid-point circumference.

Question 1080. The participant should be seated on a chair for 5 minutes before the pulse is measured. The pulse is measured for 30 seconds, multiplied by 2, and the final calculated value is recorded on the data collection form.

Questions 1090-1140. All measurements are taken while the participant is seated. The first measurement occurs after the participant has been seated on a chair for 5 minutes.

Two additional measurements are taken at 30 seconds intervals after the initial measurement. If the value is elevated, check that you are using the appropriate cuff size and try repositioning the cuff. If a participant refuses to allow a blood pressure measurement because of physical discomfort, the field should be left missing on the form and a reason indicated in the comments section 6000 at the end of the form. After data

entry is complete, data entry errors will appear for any missing blood pressure measurements. Data entry staff will be able to use the comment recorded on the form to mark the entry errors unresolvable in the Error Tracking module.

If the blood pressure is taken manually place results in the comment section of the form and also state that it is a manual blood pressure reading.

Questions 1150-1160. Record the mean of the two lowest blood pressure measurements. The mean BP is used to determine if an ALERT form is needed. If the mean BP is >180/>110, then a P1_ALERT form will need to be completed for adult participants. For pediatric participants greater than 17 years of age if BP is >140/>90, then a P2_ALERT form will need to be completed. For pediatric participants less than or equal to 17 years of age, refer to the height and gender based blood pressure norms charts to obtain blood pressure alert values.

Questions 1170-1200. These questions are completed for pediatric participants greater than 17 years of age only. Obtain the Blood Pressure Charts appropriate for age and gender of the child.

If the pediatric participant is very small and the equipment does not provide a result, a prior blood pressure reading, (i.e., measurement taken in the hospital) may be noted in the comment section of the form but those values should not be used to complete the form.

Questions 1170-1180. Record the 95th percentile blood pressure measurements for age, gender, and height. Record the systolic value in Q1170 and the diastolic value in Q1180. The reference charts are posted on the ASSESS website.

Questions 1190-1200. Record the percentile for the participant's blood pressure measurements recorded in Q1150/1160. Record the systolic percentile in Q1190 and the diastolic percentile in Q1200. The reference charts are posted on the ASSESS website. Do not record the participant's blood pressure measurements.

2.1.4 Canada Laboratory Results CBC (CAN_LABCBC)

Purpose: This form records complete blood count (CBC) based on the local laboratory results for the Canadian sites.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Complete the Visit Date as the current date the Canada Laboratory Results (CAN_LABCBC) form is completed.

This form is completed for Adult participants only.

Note: This may not necessarily be the date the blood was drawn.

Question 1000. Record the date of the blood draw. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Questions 1010-1050. Refer to the laboratory results report generated at each clinical research center's local laboratory to answer Q1010-Q1050. Each value should be rounded to the nearest decimal point or whole number, depending on the format on the form. If the values recorded from the local laboratory do not match the units, convert to the correct units or contact the local laboratory for the proper conversion.

If any values are out of range, refer to the Adult Alert (P1_ALERT) form. For values on the CBC that are outside the reference range, the coordinator should consult with the site PI to see if additional follow-up is needed. The reference ranges will be determined by the PI at the site.

If any values appear out of range based on entry errors, and the value is accurate, simply mark the appropriate error as unresolvable in the Error Tracking module, and indicate a reason why the range may be out of the limit.

Question 1050. Completed at Visit 3M ONLY.

A de-identified laboratory report should accompany the single form to the DCC.

2.1.5 Canada Serum Creatinine From Other Sources (CAN_SCR_OTHER)

Purpose: This form records any serum creatinine values obtained from other sources (other than the ASSESS-AKI Central Lab) during the outpatient phase of the study.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 12M, 24M, 36M, 48M, 60M, 72M, 84M

General Directions:

Complete the Visit Date as the current date the Serum Creatinine From Other Sources (CAN_SCR_OTHER) form is completed.

This form is completed for adult and pediatric participants who have missed an in-person visit or had a visit where a blood sample could not be collected and a serum creatinine value is found in the medical record review. Only one CAN_SCR_OTHER form should be completed per visit and the value entered should be the one that is closest to the desired visit date (even if it's before the visit). If there are multiple creatinine values on a given day, record the peak value for that day.

Q1010. If the value is determined to be an outpatient, non-emergency department test, the date of blood collection and serum creatinine value should be recorded.

A de-identified laboratory report is not required; however, the source of the value should be recorded in Q6000 of the form.

2.1.6 Concomitant Medications (CMED)

Purpose: This form records any prescription concomitant medications, calcium, Coenzyme Q10, and Vitamin D that the participant uses daily or regularly and was used within the past 30 days prior to the study contact.

Who: An ASSESS-AKI Research Coordinator completes the form as an interview.

When: Visits 3M - 90M.
Note: This form should also be updated if the participant reports a stop date for a medication between study contacts.

General Directions:

At Visit 3M, the CMED form will be initiated to record all prescription medication, Vitamin D supplement, Coenzyme Q10 supplement, or calcium supplement the participant uses daily or regularly and has taken within the last 30 days prior to the study contact. Regularly is defined as any prescription medication, Vitamin D supplement, or calcium supplement that is taken at a consistent frequency. Multivitamins are not recorded.

The brand name and generic name for each medication will be written on the paper CMED form at the time of the visit. After the visit is complete, the Research Coordinator will have two options available to assign drug codes for data entry.

- A drug codes module is available under the 'Direct Module Access' section of the data management application main menu
- Drug codes may also be searched for and assigned during the actual entry of the CMED form.

The drug code must be written on the paper form to facilitate second entry once the forms are received at the DCC. The record ID assigned to each record by the data entry application should be recorded on the paper form. After data entry is complete for the visit, an ongoing concomitant medications report may be generated to use at future visits to follow up on ongoing medications.

If a participant has not taken any medications daily or regularly within the past 30 days prior to the visit, the coordinator should complete the upper right hand header information and check the 'None' box on the form. If the 'None' box was selected for a visit, the concurrent form should still be data entered into the data entry application.

At each subsequent visit, review all ongoing medications from the ongoing concomitant medications report to collect stop dates or mark as ongoing at current visit for each medication. Collect any new medications taken daily or regularly within 30 days prior to the current study contact on a new CMED form. If a participant has not taken any concomitant medications daily or regularly within the last 30 days prior to the visit, complete the information in the upper right hand corner of the form and check 'None'. Enter the new CMED form into the study database, and if any stop dates are recorded on the ongoing concomitant medications report, these updates should be entered using the editor module. Once all new data has been entered and any stop dates updated, a new ongoing medications report will be generated for use at the next visit.

See Section 10 of the ASSESS General MOP for more information on the Ongoing Medications Report.

A Concomitant Medications (CMED) form should be completed for each participant in the study at each study contact starting with Visit 3M, even if the participant has not taken any concomitant medications daily or regularly within the past 30 days prior to the study contact.

The Concomitant Medications (CMED) forms should be data entered in the Entry module with the Entry Type of Concurrent (C) at the time the form is completed. As the participant continues through the study and medications are discontinued, the updates should be transferred from the ongoing concomitant medications report onto the data collection form and then updated in the Editor module.

If the brand name of the medication is not listed, choose another brand name associated with the generic name for that medication. Be sure to update the brand name on the CMED form to match the brand name entered into the database. If the participant is taking a generic medication and the generic name is not listed without a brand name chose one of the brand names associated with that medication. Be sure to record the brand name of the medication chosen on the CMED form to match the database entry. If a medication is not listed with a drug code, the coordinator should contact the primary data manager at the DCC.

Upon completion or early withdrawal from the study all CMED forms should be sent to the DCC for second entry.

2.1.7 Over the Counter Concomitant Medications (CMED_OTC)

Purpose: This form records any aspirin, fish oil supplements, or non-steroidal anti-inflammatory medications the participant uses daily or regularly and was used within the past 30 days prior to the study contact.

Who: An ASSESS-AKI Research Coordinator completes the form as an interview.

When: Visits 3M - 90M

Form Instructions:

Regularly is defined as any aspirin, fish oil supplement, or non-steroidal anti-inflammatory medication that is taken at a consistent frequency.

Question 1020. If necessary, allow the participant to review the CMED_OTC reference card and provide the appropriate response.

If a medication is not listed on the CMED_OTC reference card, the coordinator should contact the primary data manager at the DCC.

2.1.8 Death Record Evaluation (DEATH_EVAL)

Purpose: This form records information related to the death of a study participant.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 0 - 90M, as necessary whenever a death occurs

Form Instructions:

Complete the Visit Date as the current date the Death Record Evaluation (DEATH_EVAL) form is completed.

If the DEATH_EVAL form is completed outside of the in person visit or phone contact use the visit number closest to the date of death. If the participant has missed a visit or phone contact, these packets will need to be marked missing before the DEATH_EVAL form is entered.

Question 1040. This question records the general location of the participant's death.

- If death occurred during a hospitalization/ER visit prior to V6M, complete the DEATH_EVAL form and the WITHDR form.
- If death occurred during a hospitalization/ER visit on or after V6M complete the following forms:
  - DEATH_EVAL
  - HOSP_EVAL
  - ICD9_CPT_CODES or ICD10_CCI_CODES
    - Only **primary** ICD9 diagnosis codes and **any** Intracranial hemorrhage (ICH) codes found in the primary or secondary position should be recorded on the ICD9_CPT_CODES form.
    - All ICD9 procedure and CPT codes should be recorded on the ICD9_CPT_CODES form.
    - Only **primary** ICD10 diagnosis codes and **any** Intracranial hemorrhage (ICH) codes found in the primary or secondary position should be recorded on the ICD10_CCI_CODES form.
    - All ICD10 CCI codes should be recorded on the ICD10_CCI_CODES form.
  - INPT_CREATININE
  - WITHDR
- If death occurred outside of the hospital, the DEATH_EVAL and WITHDR forms should be completed.

2.1.9 Outpatient Dialysis Evaluation (DIAL_EVAL)

Purpose: This form is completed each time the participant reports receiving outpatient dialysis during the study.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 6M - 90M, as needed.

Form Instructions:

Dialysis in an inpatient rehabilitation unit should be considered as outpatient.

Complete the Visit Date as the current date the Outpatient Dialysis Evaluation (DIAL_EVAL) form is completed.

Question 1000 and Question 1040. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Questions 1010 -1020. A response must be selected for each modality.

Questions 1030 -1040. If the participant completely stopped dialysis in Q1030, record the date dialysis was stopped in Q1040.

2.1.10 Urine Dipstick Results (DIPSTICK)

Purpose: This form collects the results of the urine dipstick test using the Bayer Clinitek Status Analyzer.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 0, 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

After December 14, 2011, Standard urinalysis on an in-hospital (Visit 0) urine sample from non-AKI and AKI participants will be performed by the coordinators utilizing the Bayer Clinitek Status Analyzer and the DIPSTICK form will be completed.

Note: Due to some ambiguity following the decision on 12/14/2011, the UA_MICRO or DIPSTICK form may have been used. However starting on 1/16/2012, the Bayer Clinitek Status Analyzer should be used to collect results and DIPSTICK/DIPSTICK_RPT completed.

Complete the Visit Date as the current date the Urine Dipstick Results (DIPSTICK) form is completed.

A urine dipstick should be performed for all adult participants.

The pediatric participants may have these tests performed if more than 5cc of urine is available; however it is not required for the ASSESS AKI study.

Questions 1000-1070. Refer to the Bayer Clinitek Status Analyzer printout to answer Q1000-Q1070.

For values on the Dipstick that are outside the reference range, the coordinator should consult with the site PI to see if additional follow-up is needed.

A de-identified printout should accompany the form to the DCC and be placed on the Urine Dipstick Report (DIPSTICK_RPT) admin form.

2.1.11 DNA Consent (DNA_CONSENT)

Purpose: This form documents the participant's decision to allow and decline specific genetic testing to be completed.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visit 0 for pediatric participants, or Visit 3M for adult participants.

Form Instructions:

Complete the Visit Date as the current date the DNA Consent (DNA_CONSENT) form is completed.

This form is completed at V3M for adults. It is primarily completed at V0 for pediatric participants, however it can be completed as a single form V12M for pediatric participants who were enrolled prior to the consent change adding the V0 collection.

The genetic portion of the ASSESS-AKI consent should be used to complete the questions on the form.

Refer to the Biospecimen MOP for instructions (adults participants refer to sections 1 and 2; pediatric participants refer to sections 3 and 4) on the completion of DNA specimen collection forms and the entry of samples into the Biological Sample Tracking module.

Adult sites will abandon use of the DNA_CONSENT form as of June 19, 2012 and begin using the DNA_DBGAP_CONSENT form (instructions in section 2.1.11). Adult sites should maintain the DNA_CONSENT form in the study files for those enrolled prior to Site IRB approval for use of the DNA_DBGAP_CONSENT form and UW IRB certification.

2.1.12 DNA-dbGAP_Consent (DNA_DBGAP_CONSENT)

Purpose: This form documents the participant's decision to allow and decline specific genetic testing to be completed and permission for his/her genetic data to be included in the NIH Database of Genotypes and Phenotypes (dbGAP). A genetic consent form for submission to dbGaP must be signed by the participant prior to completing the DNA_DBGAP_CONSENT form.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M for adult participants.

Form Instructions:

As of June 19, 2012 this form is now being used, and the DNA_CONSENT form is no longer being used by the Adult sites.

Complete the Visit Date as the current date the DNA_dbGAP Consent (DNA_DBGAP_CONSENT) form is completed.

This form is completed as a packet form at V3M for adults only and should be used for new participants seen after the site received approval to use the DNA_DBGAP_CONSENT form.

It can also be completed at V12M, V24M, V36M, V48M, V60M, V72M, V84M as a single form when participants that were seen prior to the IRB approval for use of the DNA_DBGAP_CONSENT form are seen for follow up visits. These participants had the DNA_CONSENT form completed originally and now need to be re-consented using the DNA_DBGAP_CONSENT form.

Question 995. KAISER SITES ONLY: If re-consenting at Kaiser site, Q995 should be answered 'Yes'. Confirm consent on the DNA_CONSENT form and answer Q995 and Q1040 on DNA_DBGAP_CONSENT form. All other sites must complete all of the questions on the form.

The genetic portion of the ASSESS-AKI consent should be used to complete the questions on the form.

Refer to the Biospecimen MOP for instructions (adults participants refer to sections 1 and 2; pediatric participants refer to sections 3 and 4) on the completion of DNA specimen collection forms and the entry of samples into the Biological Sample Tracking module.

2.1.13 ECG CLINIC (ECG_CLINIC)

Purpose: This form documents the completion of an ECG during an adult in person visit and records cardiac conditions.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Complete the Visit Date as the current date the ECG Clinic (ECG_CLINIC) form is completed.

Note: This form is not used for pediatric participants or at home visits at the Yale sites. Vanderbilt and University of Washington will be completing ECGs at home visits. This form is not used for completion of an ECG related to an event.

From February 2013 to October 2, 2014, only Kaiser and University of Washington performed ECGs.

Question 1000. If ECG was not performed at this visit, complete Question 1010 and STOP completion of the form.

Question 1010. If 'Equipment failure' or 'Other' is selected to answer this question, a description should be written in the space provided on the form.

Question 1015. Response required regarding completion of the visit at a participant's home. This question is completed FOR HOME VISIT SITES ONLY.

Beginning on October 2, 2014, ECGs should be attempted at home visits.

If the Yale site performs a clinic visit where an ECG is completed, Q1015 should be answered No.

If the Yale site performs a clinic visit where an ECG is attempted, but not completed, Q1000 should be answered No and Q1010 should be completed. The remainder of the form is not completed.

Questions 1020 – 1070. Using the results of the ECG printout reading, respond to each condition. If the response to any of these questions is 'YES', please complete the ASSESS-AKI Adult Alert (P1_ALERT) form.

Questions 1080/1090. Complete the HeartSquare measurements. If unable to obtain the measurements, record '000' in the fields and record the reason why in the comment field, Q6000.

From 2/7/2013 until 10/2/2014, ECG completion was discontinued for all sites except Kaiser and UW-Harborview. After 10/2/2014, all adult sites should attempt an ECG at all clinic and home visits.

2.1.14 ECG FROM OTHER SOURCES (ECG_OTHER)

Purpose: This form documents ECGs collected from other sources.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 0 through 90M

Form Instructions:

This form is completed for adult participants who have missed an in-person visit, completed an in-person visit via phone or the ECG could not be collected and an ECG is found in the medical record review.

Complete the Visit Date as the current date the ECG From Other Sources (ECG_OTHER) form is completed.

If an ECG is present in the medical record, but is outside the visit window, the ECG should still be uploaded for overreading.

The ECGs from other sources will be uploaded to the ASSESS-AKI secure website for overreading by Wake Forest. The ECG documentation **must** be reviewed for any PHI and such information redacted prior to posting on the website. If PHI information is identified after posting, a violation may be assigned.

For more information on posting the files to the ASSESS website, please refer to the Electrocardiography Assessment Manual, The ASSESS-AKI Study.

2.1.15 Eligibility Checklist1A (ELIG1A)

Purpose: All available medical records will be reviewed and/or a participant interview will be performed to complete this form. This form determines the eligibility of a potential ASSESS-AKI participant.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visit 0

Form Instructions:

Complete the Visit Date as the current date the Eligibility Checklist (ELIG1A) form is completed in its entirety.

Note: Some information will be readily available and other information will be obtained later through review of additional medical records.

Question 1000. Kaiser, Vanderbilt, and Washington sites: Use the data collected on the BASE_CREATININE form to answer this question. If a participant has more than one available outpatient, non-emergency department test result the most recent value prior to hospitalization should be considered the baseline.

Question 1005. Yale sites: Use the data collected on the BASE_CREATININE form to answer this question. If a participant has more than one available outpatient, non-emergency department test result the most recent value prior to surgery should be considered the baseline.

Question 1010. Check N/A if the participant is in the control group. If the participant is still in the hospital and the number of days has not exceeded 90 days post AKI event, answer 'No'. The length of hospitalization will be re-assessed at Visit 3M on the ELIG2 form.

Question 1020. Check N/A if the participant is male.

Question 1040. Refer to the ASSESS-AKI protocol for the definition of baseline and the estimated GFR definition and equation.

Question 1110. If the participant has been diagnosed or treated by a doctor or other healthcare professional for metastatic or systemic cancer (excluding non-melanoma skin cancer). Response should be 'Yes' if there is a history of metastatic or systemic cancer AND they are receiving active treatment.

Question 1130. The response to this question is determined by the participant's medical record, treating physician, or clinical research center principal investigator.

Question 1140. Interventional study is defined as a study where the participant is receiving any type of study intervention. Study interventions include but are not limited to: pharmacological, mechanical, lifestyle, and educational.

Question 1160. If any of the shaded boxes are completed, the participant is ineligible. If the participant is not eligible, STOP and complete the ASSESS-AKI Withdrawal (WITHDR) form.

For more specific details pertaining to whether a Research Coordinator should permit the participant to continue in the study, see the Eligibility Criteria discussion in Section 1.

If an eligibility Protocol Exception was granted through the DCC, complete the question(s) that the exception was granted for truthfully (i.e. complete the shaded box). Q1160 should be answered 'Yes' to indicate the participant is eligible to proceed and any entry errors that result from the exception should be marked unresolvable. In the unresolvable comment section, indicate that a protocol exception was granted, who granted it, and the justification for the exception.

If the participant is eligible, continue with the rest of the Visit 0 packet.

2.1.16 Eligibility Checklist 1B (ELIG1B)

Purpose: This form is used at a phone call to confirm some eligibility criteria prior to the participant's Visit 3M.

Who: An ASSESS-AKI Research Coordinator completes this form.

When: After hospital discharge from the hospital and around 2 to 4 weeks prior to Visit 3M.

Form Instructions:

Note: This form is optional.

The Research Coordinator should refer to the Eligibility Checklist 1B Script (ELIG1B_SCRIPT) form when administering this form. Prior to the phone call, the Research Coordinator should review the visit scheduler report to obtain the desired visit date and visit window for the Visit 3M.

Complete the Visit Date as the current date the Eligibility Checklist 1B (ELIG1B) form is completed.

If the participant is eligible, confirm the Visit 3M appointment and enter the rest of the Visit 0B interim packet.

Question 1000. DO NOT ASK THIS QUESTION. If the participant is no longer living, proceed to Question 1080 and complete the ASSESS-AKI Withdrawal (WITHDR) form and the ASSESS-AKI Death Record Evaluation (DEATH_EVAL) form.

Question 1010. If the participant has been on dialysis for the past three months, complete Question 1020.

Question 1030. If the participant was enrolled in an interventional study (pharmacological, mechanical, lifestyle, educational) since discharge from the hospital, complete Question 1040.

Question 1050. If the participant has been diagnosed or treated by a doctor or other healthcare professional for metastatic or systemic cancer (excluding non-melanoma skin cancer) since hospital discharge, complete Question 1060. Response should be 'Yes' if there is a history of metastatic or systemic cancer AND they are receiving active treatment.

Question 1070. Check N/A if the participant is male.

Question 1080. If any of the shaded boxes are completed, the participant is ineligible. If the participant is not eligible, complete the ASSESS-AKI Withdrawal (WITHDR) form.
For more specific details pertaining to whether a clinic coordinator should permit the participant to continue in the study, see the Eligibility Criteria discussion in Section 1.

If an eligibility Protocol Exception was granted through the DCC, complete the question(s) that the exception was granted for truthfully (i.e. complete the shaded box). Q1080 should be answered 'Yes' to indicate the participant is eligible to proceed and any entry errors that result from the exception should be marked unresolvable. In the unresolvable comment section, indicate that a protocol exception was granted, who granted it and the justification for the exception.

2.1.17 Eligibility Checklist 2 (ELIG2)

Purpose: All available medical records will be reviewed and/or a participant interview will be performed to complete this form. This form confirms the eligibility of a potential ASSESS-AKI participant for the outpatient phase and matching.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visit 3M

Form Instructions:

Complete the Visit Date as the current date the Eligibility Checklist 2 (ELIG2) form is completed.

Question 1000. Check N/A if the participant is male.

Question 1005. Check N/A if the participant is in the control group.

Question 1010. Check N/A if the participant is in the control group.

Question 1070. Response should be 'Yes' if there is a history of metastatic or systemic cancer AND they are receiving active treatment.

Question 1080. The response to this question is determined by the participant's treating physician or clinical research center principal investigator.

Question 1090. Interventional study is defined as a study where the participant is receiving any type of study intervention. Study interventions include but are not limited to: pharmacological, mechanical, lifestyle, and educational.

Question 1110. Adult participants must be able to provide an adequate sample of blood at the 3-month visit. If the participant does not tolerate the blood draw or the technician has a difficult time obtaining the sample, the Research Coordinator should evaluate the participant's ability to provide samples throughout the study. Blood samples will be drawn again at every in-person study visit.

Adult participants should provide at least 10mL.

Check N/A for pediatric participants. There is no longer a minimum for blood samples for pediatric participants at V3M.

Question 1115. Participants must be able to provide an adequate sample of urine at the 3 month visit.

Adult participants should provide at least 20mL.

Pediatric participants wearing diapers should provide at least 1.6mL. Pediatric non-diaper wearing participants should provide at least 5mL.

Question 1120. If any of the shaded boxes are completed, the participant is ineligible. If the participant is not eligible, STOP and complete the ASSESS-AKI Withdrawal (WITHDR) form.

For more specific details pertaining to whether a Research Coordinator should permit the participant to continue in the study, see the Eligibility Criteria discussion in Section 1.

If an eligibility Protocol Exception was granted through the DCC, complete the question(s) that the exception was granted for truthfully (i.e. complete the shaded box). Q1120 should be answered 'Yes' to indicate the participant is eligible to proceed and any entry errors that result from the exception should be marked unresolvable. In the unresolvable comment section, indicate that a protocol exception was granted, who granted it and the justification for the exception.

If the participant is eligible, continue with the rest of the Visit 3M packet.

2.1.18 Hospital Record Evaluation (HOSP_EVAL)

Purpose: This form summarizes the hospital/ER visit when a participant has been hospitalized or sought care at the ER during the study.

Who: An ASSESS-AKI Research Coordinator and/or principal investigator completes this form.

When: Visits 6M - 90M, as necessary whenever a hospitalization occurs

Form Instructions:

If the HOSP_EVAL form is completed outside of the in person visit or phone contact use the visit number closest to the day the hospitalization is reported. If the participant has missed a visit or phone contact, these packets will need to be marked missing before the HOSP_EVAL form is entered.

Complete the Visit Date as the current date the Hospital Record Evaluation (HOSP_EVAL) form is completed.

Note: This may not necessarily be the date the hospitalization occurred.

Coordinators should complete a separate hospital record evaluation (HOSP_EVAL) form AND an AKI evaluation (AKI_EVAL) for each hospitalization. Admission to an inpatient rehabilitation unit or inpatient drug/alcohol treatment facility is not considered to be a hospitalization.

On March 8, 2012, the QCC deleted the AKI_EVAL as an ASSESS data collection form. The QCC is agreeable with the sites data entering AKI_EVAL for events they've completed entirely. In addition, the QCC is agreeable with all sites not data entering the AKI_EVAL for events they are still in the process of collecting records, reviewing, and/or completing forms for reported events prior to March 8, regardless of the site visit date.

The page numbers should be completed for each set of forms. For example, if the participant had two hospitalizations and the coordinator complete two forms, the pages would be numbered as follows: 1 of 6, 2 of 6, 3 of 6, 4 of 6, 5 of 6 and 6 of 6. During data entry, these fields are no longer data entered, but will populate with the correct record number.

Question 1000. If the corresponding hospitalization was documented in Question 1 on the Medical Event Questionnaire (P1_EVENTS/P2_EVENTS) form, then Q1010-Q1040 should be completed. If the response is NO, only Q1010 and Q1040 should be completed.

Questions 1010 – 1030, 1060-1070. These fields are required when completing the hospital record evaluation (HOSP_EVAL) form and an error will be displayed upon entry or the form if any of these fields are left missing. Q1010 must provide the primary reason for the hospitalization even if the hospitalization was not documented on the P1_EVENTS/P2_EVENTS form. If Q1000 is answered Yes, Q1020 and Q1030 must be completed with the admission and discharge date reported by the participant or informant. If the participant cannot remember the complete admission and/or discharge date mark the resulting error(s) unresolvable and include the partial date information in the comment. If Q1050 is answered Yes,

Q1060 and Q1070 are required. Q1060 and Q1070 must provide the admission and discharge/death dates from the medical record.

A HOSP_EVAL record should not be data entered into the database if medical records cannot be obtained.

Question 1010. Refer to the corresponding Medical Event Questionnaire (P1_EVENTS/P2_EVENTS) form for an annotation number. For example, if an adult participant was primarily hospitalized for a mini stroke and P1_EVENTS form Q1110 = 1, then 1110 would be entered into this field on the HOSP_EVAL form. If the hospitalization was not documented on the P1_EVENTS/P2_EVENTS form choose the annotation from Q1a-1k on the P1_EVENTS/P2_EVENTS form that best describes the hospitalization. If multiple events are indicated on the Medical Event Questionnaire, the Research Coordinator will evaluate all the reasons and select the annotation number corresponding to the primary reason for the hospitalization.

Questions 1020 and 1030. Record the admission and discharge dates from the Event Information Sheet (EVENT_INFO) completed in conjunction with the Medical Events (P1_EVENTS/P2_EVENTS) form. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Question 1050. If hospital records were identified and obtained, complete Q1060/1070.

Questions 1060 and 1070. Record the admission and discharge dates from the medical records. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Questions 1080, 1090, 1100, and 1105. If any qualifying ICD9/ICD10/CPT/CCI codes are present in the medical records, answer yes and complete the appropriate codes sheet.

Qualifying codes defined as:

- Only **primary** ICD9 diagnosis codes and **any** Intracranial hemorrhage (ICH) codes found in the primary or secondary position should be recorded on the ICD9_CPT_CODES form.
- All ICD9 procedure and CPT codes should be recorded on the ICD9_CPT_CODES form.
- Only **primary** ICD10 diagnosis codes and **any** Intracranial hemorrhage (ICH) codes found in the primary or secondary position should be recorded on the ICD10_CCI_CODES form.
- All ICD10 CCI codes should be recorded on the ICD10_CCI_CODES form.

If the primary code is an arrhythmia code and a procedure code is documented using a HCPSCS code, record the arrhythmia code on the appropriate code sheet and send the record to the PI to review and complete Q8 on the HOSP_EVAL form.

If the primary code is an arrhythmia code and a procedure code is not found in the record, record the arrhythmia code on the appropriate code sheet, but do not send for PI review.

If the primary code is an arrhythmia code and a procedure code is documented with a code on the ASSESS-AKI code list, record the arrhythmia code and the procedure code(s) on the appropriate code sheet.

If ICD9 codes or CPT codes are identified complete the ICD9/CPT ADMINISTRATIVE CODES (ICD9_CPT_CODES) sheet.

If ICD10 codes or CCI codes are identified complete the ICD10/CCI ADMINISTRATIVE CODES (ICD10_CCI_CODES) sheet.

For HOSP_EVAL forms completed before the new ICD9/CPT, ICD10/CCI code were available for entry on 10/23/12 and codes were available, coordinators will need to re-review records for new PVD codes if Q1170 and/or Q1250 on the P1_EVENT or Q1090 on the P2_EVENTS form is answered.

If qualifying ASSESS-AKI codes are present, stop completion of the form and begin the Event Adjudication process. Qualifying codes are defined on references cards located on the secure website.

Exception: If a code for death is the only code recorded for the event, the records should be reviewed by the investigator to determine if the event should continue to the event adjudication process.

Questions 1110-1160, 1190-1240 and 1260. If no qualifying ICD-9/ICD-10 codes are present in the medical records, the coordinator records the primary discharge diagnosis in Q6000 and the Principal Investigator completes Q1110-1160, 1190-1240 and 1260 and signs Q6000 to confirm who reviewed the chart.

For HOSP_EVAL forms completed before the addition of Q1190-Q1240 on 10/11/2012 where codes were not available and an investigator answered Q8, all records will need to be re-reviewed to look the new procedures. Data Corrections will need to be submitted to provide the responses to Q1190-Q1240 and the investigator should again sign Q6000 to confirm that the chart was re-reviewed. A new copy of the form does not need to be completed and sent to the DCC.

2.1.19 ICD9/CPT Administrative Codes Sheet (ICD9_CPT_CODES)

Purpose: This form facilitates the collection of the primary discharge diagnosis code, any Intracranial hemorrhage code and all procedure and CPT codes designated for ASSESS-AKI abstracted from medical records when a hospitalization/ER visit occurs.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 6M - 90M, as needed

Form Instructions:

If an inpatient death has been reported and no qualifying ASSESS codes are listed as the primary discharge diagnosis and the principal investigator reviews the records indicating the primary diagnosis of death, unspecified in Q6000 on the HOSP_EVAL form, the ICD9_CPT_CODES form should be completed. If the principal investigator identifies another non-ASSESS diagnosis/procedure code on the HOSP_EVAL form, an ICD9_CPT_CODES form should not be completed.

Question 1000. The admission date should match the admission date recorded in Q1060 on the Hospital/ER Evaluation (HOSP_EVAL) form.

Question 1010. Record primary discharge diagnosis code, any intracranial hemorrhage codes in the primary or secondary position, and all procedure and CPT ASSESS-AKI codes in the order that they are recorded in the medical records. Each is identified by a record ID number.

The primary discharge diagnosis and intracranial hemorrhage code distinction was effective as of April 11, 2013.

Questions 1020 - 1030. Record only 1 type of code (ICD9 or CPT) on each row of the form.

These codes will be validated against the reference cards located on the secure website. If a code found in the medical record corresponds to one of the categories on the reference card, but is not listed on the card, the coordinator should contact the primary data manager at the DCC.

2.1.20 ICD10/ CCI Administrative Codes Sheet (ICD10_CCI_CODES)

Purpose: This form facilitates the collection of the primary discharge diagnosis code, any intracranial hemorrhage (ICH) code and all procedure and CCI codes designated for ASSESS_AKI abstracted from medical records when a hospitalization/ER visit occurs.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 6M - 90M, as needed

Form Instructions:

If an inpatient death has been reported and no qualifying ASSESS codes are listed as the primary discharge diagnosis and the principal investigator reviews the records indicating the primary diagnosis of death, unspecified in Q6000 on the HOSP_EVAL form, the ICD10_CCI_CODES form should be completed. If the principal investigator identifies another non-ASSESS diagnosis/procedure code on the HOSP_EVAL form, an ICD10_CCI_CODES form should not be completed.

Question 1000. The admission date should match the admission date recorded in Q1060 on the Hospital/ER Evaluation (HOSP_EVAL) form.

Question 1010. Record the primary discharge diagnosis code, any intracranial hemorrhage codes in the primary or secondary position and all procedure and CCI ASSESS-AKI codes in the order that they are recorded in the medical records. Each is identified by a record ID number.

The primary discharge diagnosis and intracranial hemorrhage code distinction was effective as of April 11, 2013.

Questions 1020 - 1030. Record only 1 type of code (ICD10 or CCI) on each row of the form. When recording the code for Q1020 on the paper form and when completing entry into the database the coordinator will need to add the decimal point in the appropriate spot as needed. The form is not formatted to include the decimal point because the field accepts letters as well as numbers.

These codes will be validated against the reference cards located on the secure website. If a code found in the medical record corresponds to one of the categories on the reference card, but is not listed on the card, the coordinator should contact the primary data manager at the DCC.

2.1.21 Inpatient Serum Creatinine Measures (INPT_CREATININE)

Purpose: This form records all inpatient serum creatinine measurements during a hospitalization

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 0 and 6M - 90M, as needed

Form Instructions:

Complete the Visit Date as the current date the Inpatient Serum Creatinine Measures (INPT_CREATININE) form is completed in its entirety (after all values have been collected and recorded).

Only serum creatinine values obtained at an IDMS standardized laboratory will be recorded on this form and entered into the data entry application.

Question 1000. Assign a Collection Number to each serum creatinine value obtained from the medical records beginning with the number 01. Each measurement should have a unique collection number. If a measurement is removed after numbering is complete, cross out the information for the row. The collection numbers do not need to be adjusted.

Question 1010. Collection date is a part of the definition of a unique record along with the collection number; therefore a collection will be identified by the collection date and collection number. If there are multiple creatinine values on a given day, record the peak value within the 24 hour period. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Question 1020. Record the time serum creatinine samples were collected using a 24- hour clock. During data entry, do not enter a colon ':' symbol, just the numbers. Example: 1515, not 15:15. If the coordinator cannot find a time when completing the chart review for the creatinine values, use 0000 as the time the specimen was collected.

Question 1030. Round the value to the nearest ten hundredths of a decimal. During data entry, remember to enter the decimal place into the field. Example, enter 001.11 instead of just 00111.

Question 1040. The unit mg/dL has been designated as the accepted measurement for the United States sites and umol/L has been designated as the accepted measurement for the Canadian sites.

Question 6000. The comment section for this form will also only be entered once during entry of the first record. The comment for the first record will auto-populate for each additional record that is entered.

For more specific details pertaining to the inpatient serum creatinine, see the Inpatient Serum Creatinine discussion in Section 1.

2.1.22 Modified Mini-Mental State Exam (MMMSE)

Purpose: This test is administered to the participant to assess his/her cognitive function status. This exam is given to adult participants only.

Who: An ASSESS-AKI Research Coordinator completes the form (interviews participant).

When: Visits 3M, 12M, 36M

Form Instructions:

Complete the Visit Date as the current date the Modified Mini-Mental State Exam (MMMSE) form is completed.

Refer to the Quality of Life and Cognitive Function Manual, MMMSE, for detailed instructions on preparation, administration, and scoring of the questionnaire.

This form will not be entered into the database. The scores from the Modified Mini-Mental State Exam (MMMSE) will be transcribed onto the Modified Mini-Mental State Exam Tally (MMMSE_TALLY) Sheet and entered into the database.

The Modified Mini-Mental State Exam (MMMSE) form and Modified Mini-Mental State Exam Tally Sheet (MMMSE_TALLY) form will be sent to the DCC. The DCC will randomly select a portion of the Modified Mini-Mental State Exams (MMMSE) forms to audit the accuracy of the scores reported on the Modified Mini-Mental State Exam Tally Sheet (MMMSE_TALLY) form

If the DCC discovers the scores on the Modified Mini-Mental State Tally Sheet do not match the Modified Mini-Mental State Exam form, the DCC will inform the QCC committee. The Modified Mini-Mental State Exam form is already pre-coded to allow entry, if necessary.

2.1.23 Modified Mini-Mental State Exam Phone (MMMSE_PHONE)

Purpose: This test is administered to the participant to assess his/her cognitive function status. It is used when the participant cannot complete a visit in the clinic and it is designed to be administered over the phone. This exam is given to adult participants only.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M, 12M, 36M

Form Instructions:

Method of administration for this form must stay the same during the study visit. Mode of administration may change between visits but not during a visit. The phone version of the Modified Mini-Mental State Exam is only available for US participants only.

Complete the Visit Date as the current date the Modified Mini-Mental State Exam Phone (MMMSE_PHONE) form is completed.

Refer to the Quality of Life and Cognitive Function Manual, MMMSE Telephone, for detailed instructions on preparation, administration, and scoring of the telephone questionnaire.

This form will be completed by the Research Coordinator when the participant cannot complete the visit in person and it is administered over the phone.

This form will not be entered into the database. Only the scores from the Modified Mini-Mental State Exam Phone (MMMSE_PHONE) form will be transcribed onto the Modified Mini-Mental State Exam Phone Tally Sheet (MMMSE_TALLY_PHONE) and entered into the database.

The Modified Mini-Mental State Exam Phone (MMMSE_PHONE) form and Modified Mini-Mental State Exam Phone Tally Sheet (MMMSE_TALLY_PC) form will be sent to the DCC. The DCC will randomly select a portion of the Modified Mini-Mental State Exam Phone (MMMSE_PHONE) forms to audit the accuracy of the scores reported on the Modified Mini-Mental State Exam Phone Tally Sheet (MMMSE_TALLY_PC) form

If the DCC discovers the scores on the Modified Mini-Mental State Phone Tally Sheet do not match the Modified Mini-Mental State Exam Phone form, the DCC will inform the QCC committee. The Modified Mini-Mental State Phone Exam form is already pre-coded to allow entry, if necessary.

2.1.24 Modified Mini-Mental State Exam Tally Sheet (MMMSE_TALLY)

Purpose: This form is used to record the scores from each section of the Modified Mini-Mental State Exam.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M, 12M, 36M

Form Instructions:

Complete the Visit Date as the current date the Modified Mini-Mental State Exam Tally (MMMSE_TALLY) sheet is completed.

Note: This may not necessarily be the date the MMMSE form was completed.

Questions 1000-1160. Record the values from the corresponding section totals on the Modified Mini-Mental State (MMMSE) form. Only section totals will be recorded and entered into the database.

The Modified Mini-Mental State Exam (MMMSE) form and Modified Mini-Mental State Exam Tally Sheet (MMMSE_TALLY) form will be sent to the DCC. The DCC will randomly select a portion of the Modified Mini-Mental State Exams (MMMSE) forms to audit the accuracy of the scores reported on the Modified Mini-Mental State Exam Tally Sheet (MMMSE_TALLY) form.

2.1.25 Modified Mini-Mental State Exam Tally Sheet (MMMSE_TALLY_PC)

Purpose: This form is used to record the scores from each section of the Modified Mini-Mental State Exam Phone form.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M, 12M, 36M

Form Instructions:

Complete the Visit Date as the current date the Modified Mini-Mental State Exam Phone Tally (MMMSE_TALLY_PC) sheet is completed.

Note: This may not necessarily be the date the MMMSE_PHONE form was completed.

Questions 1000-1130. Record the values from the corresponding section totals on the Modified Mini-Mental State Exam Phone (MMMSE_PHONE) form. Only section totals will be recorded and entered into the database.

The Modified Mini-Mental State Exam Phone (MMMSE_PHONE) form and Modified Mini-Mental State Exam Phone Tally Sheet (MMMSE_TALLY_PC) form will be sent to the DCC. The DCC will randomly select a portion of the Modified Mini-Mental State Exam Phone (MMMSE_PHONE) forms to audit the accuracy of the scores reported on the Modified Mini-Mental State Exam Phone Tally Sheet (MMMSE_TALLY_PC) form.

2.1.26 Outpatient Vascular Procedure Evaluation (OUTPT_VASC)

Purpose: This form is completed when a percutaneous coronary intervention or cardiac catherization as an outpatient vascular procedure is reported by the participant or discovered during a review of the medical records. Canadian sites will not complete this form because these procedures are not performed at outpatient surgical centers.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 6M - 90M, as needed.

Form Instructions:

Complete the Visit Date as the current date the Outpatient Vascular Evaluation (OUTPT_VASC) form is completed.

Question 1000. Record the number of percutaneous coronary interventions (PCI) the participant has had since the last ASSESS AKI study contact. If the number of PCIs in more than 3, record the 3 most recent procedures in Q1010-1030.

Questions 1010 - 1030. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

2.1.27 Procedure Investigation (PI)

Purpose: This form is completed when a surgery, balloon angioplasty, or stent as an outpatient vascular procedure is reported by the participant or discovered during a review of the medical records.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 6M - 90M, as needed.

Form Instructions:

Complete the Visit Date as the current date the Procedure Investigation (PI) form is completed.

Question 1000. Record the date that the test/procedure was performed. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Questions 1010-Q1020. Answer both questions, but answer 'Yes' to only one of the procedures/treatments per form. Complete a separate PI form for each procedure/treatment. A PI form should not be data entered into the database if medical records cannot be obtained.

The page numbers should be completed for each form. For example, if the participant had two procedures/treatments and the coordinator completes two forms, the pages would be numbered as follows: 1 of 2 and 2 of 2. During data entry, these fields are no longer data entered, but will populate with the correct record number.

2.1.28 Short Physical Exam (SEXAM)

Purpose: This form collects height and weight data for all participants, as well as height and weight percentiles for pediatric participants.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Complete the Visit Date as the current date the Short Physical Exam (SEXAM) is completed.

Question 1000. If the participant is able to stand for height and weight measurements, record the value in Q1010 and Q1020.

Questions 1030-1050. If the participant is unable to stand for height and weight measurements and reports height and weight in US units of measurement, complete questions 1030 -1050.

Questions 1060-1070. If the participant is unable to stand for height and weight measurements and reports height and weight in metric units of measurement, complete questions 1060 and 1070. If the participant is an infant or toddler who cannot stand, supine length will be measured by a measuring tape.

Question 1080. Complete this question only if the participant is unable to stand for height and weight measurements (response to Q1000 is NO).

Questions 1090-1100. These questions are completed for pediatric participants less than or equal to 18 years of age only. Obtain height/weight charts appropriate for the age and gender of the child. The reference charts are posted on the ASSESS website.

2.1.29 SF-12 Health and Well-being (SF-12)

Purpose: The SF-12v2™ Health Survey is a 12-item subset of the SF-36v2™ that is a brief, reliable measure of overall health status. This form is completed by adult participants only.

Who: The participant completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Offer the self-administered survey to the participant. It should take about 2 minutes for the participant to complete the survey.

Ask the participant to read the instructions and answer the 7 questions.

Place participant's label on the survey AFTER the participant has completed the survey. A label template using Microsoft Word will be posted on the ASSESS-AKI secure website. These labels will print out one entire sheet of labels per participant, so it is suggested that only the Participant ID and Initials be populated on these labels. The visit number, visit date, and coordinator ID can be hand written therefore allowing the use of these labels for QOL instruments throughout the study.

Place the remaining labels in the participant's study folder for use at each visit.

2.1.30 Trails B Scoring (TRAILSB_SCORE)

Purpose: This form records the results of the self-administered TRAILS B survey.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visit 3M, 12M, 24M, 36M

Form Instructions:

Question 1000. Record the number of years of school the participant has completed. If the participant has a GED = 12 years

Question 1010. Record the number of seconds required for the participant to complete the task.

If the participant has not completed the test after 5 minutes, stop the test and enter '999' for Q1010.

2.1.31 Urinalysis Micro (UA_MICRO)

Purpose: This form records the date of urine collection and the urinalysis microscopy and urine dipstick values for the inpatient phase.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visit 0 (if visit occurs on or before December 14, 2011)

Form Instructions:

A urinalysis micro and urine dipstick should be performed for all adult participants seen on or before December 14, 2011.

After December 14, 2011, microscopy is no longer mandatory for ASSESS participants. Standard urinalysis on an in-hospital urine sample from non-AKI and AKI participants will now be performed by the coordinators utilizing the Bayer Clinitek Status Analyzer. The UA_MICRO form will not be used for any visits occurring after December 14, 2011.

Note: Due to some ambiguity following the decision on 12/14/2011, the UA_MICRO or DIPSTICK form may have been used. However starting on 1/16/2012, the Bayer Clinitek Status Analyzer should be used to collect results and DIPSTICK/DIPSTICK_RPT completed.

The pediatric participants may have these tests performed if more than 5cc of urine is available; however it is not required for the ASSESS AKI study.

The UA_MICRO form is a single form at Visit 0. If the urinalysis micro and urine dipstick tests are not completed, select 'NO' on the Inpatient Visit Procedure Checklist (INPTATIENT_CHK) and write a comment indicating why it was not completed. If less than 5cc of urine was collected for the pediatric participant, select 'N/A'.

Complete the Visit Date as the current date the Urinalysis Micro (UA_MICRO) form is completed.

Note: This may not necessarily be the date the urine was collected.

Question 1000. Record the urine collection date.

Questions 1010-1080. Record the urine dipstick values. Only one response should be checked for each question.

Q1090. If a microscopy was not requested, STOP HERE.
If no urine microscopy is performed due to a negative (or clean) dip, Q1090 should be answered 'Yes', Q1100-1170 should be answered 'less than 5' and Q1180 should be answered 'No'.

Question 1100-1120. Record the cell/hpf values. Only one response should be checked for each question.

Question 1130-1170. Record the cast/lpf values. Only one response should be checked for each question.

Question 1180. Record whether Amorphous Sediment was detected in the sample. Question must be completed with 'Yes' or 'No' response.

2.1.32 United States Laboratory Results CBC (US_LABCBC)

Purpose: This form records complete blood count (CBC) based on the local laboratory results for the US sites.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Complete the Visit Date as the current date the United States Laboratory Results (US_LABCBC) form is completed.

This form is completed for Adult participants only.

Note: This may not necessarily be the date the blood was drawn.

Question 1000. Record the date of the blood draw. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Questions 1010-1050. Refer to the laboratory results report generated at each clinical research center's local laboratory to answer Q1010-Q1050. Each value should be rounded to the nearest decimal point or whole number, depending on the format on the form. If the values recorded from the local laboratory do not match the units, convert to the correct units or contact the local laboratory for the proper conversion.

If any values are out of range for 1010-1040, refer to the Adult Alert (P1_ALERT) form. For values on the CBC that are outside the reference range, the coordinator should consult with the site PI to see if additional follow-up is needed. The reference ranges will be determined by the PI at the site.

If any values appear out of range based on entry errors, and the value is accurate, simply mark the appropriate error as unresolvable in the Error Tracking module, and indicate a reason why the range may be out of the limit.

A de-identified laboratory report should accompany the single form to the DCC.

2.1.33 United States Serum Creatinine From Other Sources (US_SCR_OTHER)

Purpose: This form records any serum creatinine values obtained from other sources (other than the ASSESS-AKI Central Lab) during the outpatient phase of the study.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 12M, 24M, 36M, 48M, 60M, 72M, 84M

General Directions:

Complete the Visit Date as the current date the Serum Creatinine From Other Sources (US_SCR_OTHER) form is completed.

This form is completed for adult and pediatric participants who have missed an in-person visit or had a visit where a blood sample could not be collected and a serum creatinine value is found in the medical record review. Only one US_SCR_OTHER form should be completed per visit and the value entered should be the one that is closest to the desired visit date (even if it's before the visit). If there are multiple creatinine values on a given day, record the peak value for that day.

Q1010. If the value is deteremined to be an outpatient, non-emergency department test, the date of blood collection and serum creatinine value should be recorded.

A de-identified laboratory report is not required; however, the source of the value should be recorded in Q6000 of the form..

2.1.34 Withdrawal (WITHDR)

Purpose: This form records the withdrawal date, primary reason for the participant's withdrawal from the study, and documentation of disposed specimens.

Who: The ASSESS-AKI Research Coordinator completes the form.

When: It is completed at the study visit when a participant completes or withdrawals from the study (Visits 0-69M).

Form Instructions:

The Withdrawal (WITHDR) form must be completed for every participant who is enrolled in the ASSESS-AKI when he/she departs from the study.

If the WITHDR form is completed outside of the in person visit or phone contact use the visit number closest to the day the withdrawal occurred. If the participant has missed a visit or phone contact, these packets will need to be marked missing before the WITHDR form is entered.

Complete the Visit Date as the current date the Withdrawal (WITHDR) form is completed.

Question 1000. Only answer 'Yes' if the participant has completed the study, otherwise answer 'No'.

Question 1010. Even if there are multiple reasons for withdrawal, indicate the primary reason for withdrawal from the study.

Question 1020. Record the date of completion/withdrawal. If the participant dies in between the completion of the Inpatient Checklist 2 and the 3M visit, this date should represent the date the participant died. During data entry, the '/'s can either be entered or left missing as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

If the participant is withdrawn due to ineligibility at V3M (option 5 is selected in Q1010) the date withdrawn should correspond with the date the V3M P1/P2_EVENTS form is completed (visit date).

Question 1030. Participants have the option to request the disposal of specimens stored for future analysis. If Q1030 is answered 'Yes', indicate in questions 1040-1060 which specimens the participant wants removed. The Research Coordinator is responsible for disposing of the specimens stored at the clinical research site. The DCC will notify in writing the central laboratory and the NIDDK Repository of the participant's request.

When a participant withdraws from the study, complete/enter a Withdrawal (WITHDR) form as soon as possible and send the WITHDR form and CMED forms to the DCC on your next regular shipment day. No additional data may be collected after the withdrawal visit date or this will result in a protocol violation.

2.2 ADULT PROTOCOL SPECIFIC DATA COLLECTION FORMS

Adult protocol specific data collection forms are located on the ASSESS-AKI secure website. Individual forms are posted in alphabetical order by form code in the Individual Forms folder.

When preparing for a visit, the Research Coordinator will print a complete visit packet from a center specific folder located in Protocols:Forms:Adult (P1): Visit Packets. Each visit packet will begin with a data processing cover sheet, followed by the visit procedure checklist, and each form (standard or protocol specific) to be used during the visit.

Visit packets posted on the website have been programmed to allow header information to be pre-filled on each page prior to printing the packet. Using the pre-fill option will ensure each page identifies a participant ID in the event forms become dislodged from the packet.

2.2.1 Adult Alert (P1_ALERT)

Purpose: This form for the adult participant identifies potential serious medical problem(s) such as change in blood pressure, acute distress symptoms, and changes in laboratory results or ECG results.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M - 90M, as necessary upon identification of alert information associated with ASSESS study visits and tests.

Form Instructions:

Complete the Visit Date as the current date the Adult Alert (P1_ALERT) is completed.

If the alerts happen on different days, multiple P1_ALERT forms would be used. For example, there would be multiple alert forms completed related to an elevated BP reading and an out-of-range lab value. The BP value would be recorded on the visit date when the blood pressure reading is taken and recorded and the coordinator notes the value is out-of-range. The lab value would be recorded on the date that the results are received from the lab and an out-of- range value is reported.

If more than one alert happens on the same day, those alerts would be recorded on one P1_ALERT form, For example, an elevated blood pressure reading is noted, and the participant also has symptoms of acute distress. Both of these are noted in the clinic on the day of the visit and would be recorded on one P1_ALERT form.

Question 1000. The date of the alert could be the date of the ASSESS study visit or the date when laboratory or ECG results are received. For example, if a laboratory value indicates an alert, use the date the laboratory report was received as the Date of Alert Value(s).

Question 1010. If the alert is due to a change in blood pressure, complete Q1020 and Q1030. If No, proceed to Q1040.

Question 1040. If the alert is due to acute distress, complete Q1050 – Q1080. If No, proceed to Q1090.

Questions 1050-1080. Acute distress is identified by three items – chest pain, severe respiratory distress, and acute neurological symptoms. Other symptoms determined as acute by the Principal Investigator or the Research Coordinator are noted under “Other” category and specified in the space provided.

Question 1090. If the alert is due to laboratory results, complete Q1100 – Q1160. If No, proceed to Q1170. Central Lab results are used for the alert values with the exception of the CBC Hemoglobin.

Questions 1100-1150. Laboratory results identified as outside the values listed on the Adult Alert (P1_ALERT) form will be checked ’Yes’, and all values within the range are checked ’No’.

Question 1140. For the outpatient annual visits, the value from the Central Lab of the previous ASSESS visit is used to determine a doubling of the serum creatinine. For V3M, Kaiser and Vanderbilt use the

outpatient baseline value from V0 to check for serum creatinine doubling at V3M. Yale London Ontario uses the creatinine at discharge for the V0 vs. V3M comparisons.

For values on the CBC and/or Dipstick that are outside the reference range, the coordinator should consult with the site PI to see if additional follow-up is needed.

Question 1160. Laboratory results, other than those listed on the data collection form, determined as abnormal are noted as "Other" and identified in the space provided.

Question 1170. If an alert is due to ECG results, complete Q1180 – Q1280. If No, proceed to Q1290.

Question 1180. The date of the reading is the date the ECG was read to identify abnormalities. If the ECG was read at the ECG Central Reading Center, record the read date from the reading center report. If the ECG was read at a local facility, the read date will be found on the ECG report.

Question 1190. Indicate whether the reading was done at a local reading center or the ECG Central Reading Center.

Question 1290. Indicate if the Research Coordinator notified the Principal Investigator of the alert(s).

Question 1300. Indicate the action taken following the review of alert(s). If 'Other' is selected, a description should be provided on the form.

Question 1310. Indicate if the participant was made aware of the medical alert. It is the responsibility of the Research Coordinator and/or the Principal Investigator to decide when/if to inform the participant of the outcome.

Select 'N/A' if the participant is deceased or lost to follow up.

2.2.2 Adult Medical Event Questionnaire (P1_EVENTS)

Purpose: This form for the adult participant collects information about the frequency of hospitalizations/ER visits related to specific medical conditions, indicates if specific tests/procedures were performed, and documents the death of a participant.

Who: An ASSESS-AKI Research Coordinator completes the form as an interview.

When: Visits 3M-90M

Form Instructions:

Complete the visit date as the current date the Adult Events Questionnaire (P1_EVENTS) form is completed.

If the P1_EVENTS form is completed outside of the in person visit or phone contact use the visit number closest to the day the event is reported. If the participant has missed a visit or phone contact, these packets will need to be marked missing before the single P1_EVENT form is entered.

For example, if a death is reported and the last visit completed was V6M and the death occurred near the 24M visit, the V12M, V18M visits will need to be set to missing in the database before the V24M P1_EVENTS form can be data entered.

The Research Coordinator completes this questionnaire as an interview with the participant. Prior to the phone call or visit, the Research Coordinator should complete the date of the last study contact in the shaded box. This date will help the participant focus on the time period between the last study contact and the current contact.

If the participant is unsure if an event was previously reported at a study contact, the Research Coordinator should record the event and confirm the event through review of medical records and past Event Information Sheets (EVENT_INFO) forms.

Questions 1000-1220. If 'Yes' is checked for a hospitalization or emergency room visit for any medical problems in Q1000, each subsequent item requires a 'Yes' or 'No' response, and the number of hospitalizations or ER visits per event. Admission to an inpatient rehabilitation unit or drug/alcohol treatment facility is not considered to be a hospitalization.

If 'No' is checked in response to Q1000, proceed to Question 1250.

Question 1050. This question is asking about pulmonary edema. Thoracentesis performed in a doctor's office would be considered a 'No' response.

Questions 1210-1220. If the medical condition/problem does not fit into any of the listed categories in Q1010 – Q1200, check Q1210 for 'other' and list the number of ER visits/hospitalizations that fall under this category.

Question 1230. The Research Coordinator determines the number of separate hospitalizations, based on the 'Yes' responses by the participant in Q1010 – Q1220 and review of medical records.

Note: Some conditions may have occurred during the same hospitalization.

The Research Coordinator must complete the Event Information Sheet (EVENT_INFO) form and the Hospital/ER Record Evaluation (HOSP_EVAL) form for each separate hospitalization/ER visit except when death occurs outside of the hospital and is reported by proxy.

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Exceptions: If the ER visit lasts <23 hours and did not required admission, a HOSP_EVAL form should not be completed. If a hospitalization lasts <23 hours, a HOSP_EVAL form should not be completed. If an event meets either of these two criteria, this information may be entered into Q6000 on the P1_EVENTS form (if the form is still present at the center) or documented in the participant study file for reference to any queries sent by the DCC.

Questions 1250-1280. If any of the surgery types listed were performed, indicate the setting where these surgeries were performed in Q1260/Q1280.

Question 1290. The Research Coordinator determines the number of tests or procedures completed, based on the 'Yes' responses by the participant in Q1250 and Q1270 and the review of medical records.

The Research Coordinator must complete an Event Information Sheet (EVENT_INFO) form for each test or procedure performed. If the test or procedure was completed as an inpatient procedure, the Hospital/ER Record Evaluation (HOSP_EVAL) form *may* be completed. During review of medicals records, if the coordinator finds the test/procedure is already documented on a HOSP_EVAL form in response to Question 1, a separate HOSP_EVAL form is not required. A Procedure Investigation (PI) form should be completed for each outpatient procedure(s).

Questions 1310 - 1340. If any of the procedures listed were performed, indicate the setting where the procedures were performed in Q1320/Q1340.

Question 1350. The Research Coordinator determines the number of tests or procedures completed, based on the 'Yes' responses by the participant in Q1310 and Q1330 and the review of medical records.

The Research Coordinator must complete an Event Information Sheet (EVENT_INFO) form for each test or procedure performed. The Hospital/ER Record Evaluation (HOSP_EVAL) *may* be completed for all inpatient procedures. During review of medicals records, if the coordinator finds the test/procedure is already documented on a HOSP_EVAL form in response to Question 1, a separate HOSP_EVAL form is not required. An Outpatient Vascular Procedure Evaluation (OUTPT_VASC) forms should be complete for outpatient procedures.

Question 1370. If the treatment type listed was performed, indicate the setting where the treatment was performed in Q1380.

Question 1390. The Research Coordinator determines the number of treatments completed, based on the 'Yes' responses by the participant in Q1370 and the review of medical records.

For participants who answer Yes to Q1370 on the Adult Medical Event Questionnaire (P1_EVENTS) as having received dialysis, a course of dialysis (having a start/stop date) is counted as one when answering Q1390 on the Adult Medical Event Questionnaire (P1_EVENTS). Each day of the dialysis should not be counted; it is the number of dialysis courses that should be counted.

The Research Coordinator must complete an Event Information Sheet (EVENT_INFO) form for each test or procedure performed. The Hospital/ER Record Evaluation (HOSP_EVAL) form *may* be completed for all inpatient treatments. During review of medicals records, if the coordinator finds the test/procedure is already documented on a HOSP_EVAL form in response to Question 1, a separate HOSP_EVAL form is not required. A Dialysis Evaluation (DIAL_EVAL) form is completed for all outpatient treatments. Dialysis in an inpatient rehabilitation unit should be considered as outpatient.

Questions 1400-1410. If death is reported, indicate the name of the informant in the space provided and the date of death.

If the death occurred during an ER visit lasting less than 23hrs, a HOSP_EVAL form should be completed.

If death is reported, the Research Coordinator must complete the ASSESS-AKI Withdrawal (WITHDR) form and the Death Record Evaluation (DEATH_EVAL) form.

2.2.3 Adult Inpatient Checklist 1 (P1_INPATIENT1)

Purpose: This form records the adult participant's past medical history, smoking history, renal medical history, baseline creatinine value, and pre-admission medication use. The information will be collected using chart review and participant self-report.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visit 0

Form Instructions:

Complete the Visit Date as the current date the Adult Inpatient Checklist 1 (P1_INPATIENT1) form is completed.

Note: This may not necessarily be the date the checklist was initiated. If the information remains unknown after a chart review and participant interview, mark 'Unknown' if that response is available.

Question 1000. If the response to Q1000 is 'Yes', complete question 1010.

Question 1110. If the response to Q1110 is 'Yes', complete question 1120.

Question 1130. If the response to Q1130 is 'Yes', complete question 1140.

Questions 1150-1170. Check 'Yes' or 'No' to each response.

Question 1180. This value should be obtained from the BASE_CREATININE form. Round the value to the nearest ten hundredths decimal place. If a participant has more than one available outpatient, non-emergency department test result the most recent value prior to hospitalization should be considered the baseline.

Question 1190. The unit mg/dL has been designated as the accepted measurement for the United States sites and umol/L has been designated as the accepted measurement for the Canadian sites.

Question 1200. Do not complete this question for control participants. The date of AKI episode is the date that the participant first qualifies as AKI per our criteria.

For more specific details pertaining to past medical history and renal medical history, see Medical History and Visit Zero in Section 1.

2.2.4 Adult Inpatient Checklist 2 (P1_INPATIENT2)

Purpose: This form evaluates the adult participant's medications given during hospitalization, in hospital exposures and complications, dialysis, ICU, and length of hospital stay.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: After the participant is discharged from the hospital (Visit 0)

Form Instructions:

Complete the Visit Date as the current date the Adult Inpatient Checklist 2 (P1_INPATIENT2) form is completed.

Note: This may not necessarily be the date the checklist was initiated. If the information remains unknown after a chart review and participant interview, mark 'Unknown' if that response is available.

Questions 1000-1060. Complete these questions at or after discharge based on any medications given anytime during the entire hospitalization.

Question 1070. If the response to Q1070 is 'Yes', complete questions 1080 - 1090.

Question 1100. Complete this question for CASE participants only.

Question 1120. Complete 'Yes' if the participant returned to the OR after the original surgery.

Question 1130. Complete this question for CASE participants only. If the response to Q1130 is 'Yes', complete questions 1140 - 1170.

Question 1170. If the response to Q1170 is 'Yes', please specify the other surgical procedure.

Question 1230. If the response to Q1230 is 'Yes', complete questions 1240 - 1310.

Questions 1240-1250, 1300-1310, and Q1330-1340. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Question 1250. Stop date for last dialysis will remain missing if participant is discharged from the hospital requiring dialysis treatment.

Question 1320. A 24-hour period is equal to 1 day, except if the last day is < 24 hours, than count that last day as 1 day.

For more specific details pertaining to medications, in hospital exposures/complications or physiological data, see Medical History and Visit Zero in Section 1.

2.2.5 Adult Demographics Information (P1_INPT_DEMO)

Purpose: This form collects inpatient demographic information on the adult participant's living arrangements, employment, healthcare, and income at the index hospitalization.

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visit 0

Form Instructions:

Complete the Visit Date as the current date the Adult Demographics Information (P1_INPT_DEMO) form is completed.

If the situation warrants, please refer the participant to the P1_INPT_DEMO_REF cards to complete this form.

Question 1050. If necessary, use CARD A of the P1_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response.

Question 1060. If necessary, use CARD B of the P1_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response. During data entry, only one response can be captured in the database. Remind the participant to ONLY select his/her primary employment status.

Primary employment status is defined as the employment type that represents greater than 50% of the person's professional activities during the past year. If he/she is in school as well as employed full time, instruct him/her to select his/her desired choice.

If the participant is on temporary medical leave, proceed to Q1090.

If the participant is a high school student, post high school student, has never worked or he/she doesn't wish to answer proceed to Q1100. Otherwise, if the participant has worked, complete questions 1070-1090.

Question 1090. If necessary, use CARD C of the P1_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response.

Questions 1070 and 1080. If participant is unsure of his/her last date of employment, explain to him/her to give a best estimate as to when he/she was last employed. The responses to Q1070 and Q1080 should make a partial date in the format of MM/YYYY. If the requested month and/or year is unknown of last employed, coordinators will use 98 for month and 9898 for year.

Questions 1100 - 1200. FOR US SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. If necessary, use CARD D of the P1_ INPT_DEMO_REF reference card for him/her to review and provide the appropriate response. A participant must select 'Yes' to at least one option.

The coordinator should make every effort to identify the type of insurance the participant has before selecting the 'Other' option. For example if the participant has Blue Cross/Blue Shield, determine with the participant whether they have an HMO version of the Blue Cross or not. If the insurance plan is a standard Blue Cross that is not an HMO, select 'Yes' for Q1130 and if they indicate the Blue Cross plan is an HMO select 'Yes' for Q1140.

If Q1200 is answered 'Yes', please write the name of the insurance on the descriptive line provided.

Questions 1210 and 1220. FOR CANADIAN SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. The participant must select one of these options.

Question 1230. If necessary, use CARD E of the P1_ INPT_DEMO_REF reference card for him/her to review and provide the appropriate response.

For more specific details pertaining to completion of the form, see Demographics and Visit Zero in Section 1.

2.2.6 Adult Lifestyle (P1_LIFESTYLE)

Purpose: This form collects information on the adult participant's history of smoking, alcohol use, recreational drug use, and current health insurance during the yearly, in-person visits.

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visits 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Complete the Visit Date as the current date the Adult Lifestyle (P1_LIFESTYLE) form is completed.

Prior to the study visit, the Research Coordinator should complete the date of the last study visit in the shaded box.

If the Research Coordinator completes this questionnaire as an interview with the participant, the participant is reminded of the date of the last ASSESS-AKI Study Visit frequently to keep the participant focused on the covered time period.

If the situations warrants, please refer the participant to the P1_LIFESTYLE reference cards to complete this form.

Question 1000. If the response to Q1000 is 'Yes', complete questions 1010 – 1040.

Question 1030. Round this value to the nearest tenth of a decimal.

Question 1040. If the response is unknown, enter 98 for the value.

Question 1050. If the response to Q1050 is 'Yes', complete questions 1060 – 1090.

Questions 1080/1090. If the participant smokes cigars, but does not smoke daily and does not know how to answer these questions, please leave Q1080 and Q1090 missing in the database. Please note the amount/frequency of cigar smoking as reported by the participant in Q6000. The entry errors for the missing values will need to mark as unresolvable.

Question 1080. Round this value to the nearest tenth of a decimal.

Question 1090. If the response is unknown, enter 98 for the value.

Question 1100. The term regularly means at least two pipefuls of tobacco a week, almost every week. If the response to Q1100 is 'Yes', complete questions 1130 and 1140.

Question 1130. Round this value to the nearest tenth of a decimal.

Question 1140. If the response is less than 1 per day, record and enter 00 for the value.

Question 1170. If the response to Q1170 is 'Yes', complete questions 1180 – 1220.

Question 1180. If necessary, use CARD A of the P1_LIFESTYLE reference card for him/her to review and provide the appropriate response.

Questions 1190 and 1200. If necessary, use CARD B of the P1_LIFESTYLE reference card for him/her to review and provide the appropriate response.

Question 1210. FOR MEN ONLY. If necessary, use CARD C of the P1_LIFESTYLE reference card for him to review and provide the appropriate response. The participant must select only one response.

Question 1220. FOR WOMEN ONLY. If necessary, use CARD C of the P1_LIFESTYLE reference card for her to review and provide the appropriate response. The participant must select only one response.

Question 1230. If the response to Q1230 is 'Yes', complete question 1240.

Question 1250. If the response to Q1250 is 'Yes', complete question 1260.

Question 1270. If the response to Q1270 is 'Yes', complete question 1280.

Question 1290. If the response to Q1290 is 'Yes', complete question 1300.

Question 1310. If Research Coordinator completed, and Q1310 is 'Yes', have the participant specify the other street drugs and record this in the space provided. If the response to Q1310 is 'Yes', complete question 1320.

Question 1330. If the response to Q1330 is 'Yes', complete questions 1340 – 1440 for the US sites and complete questions 1450-1460 for the Canadian sites.

Questions 1340 - 1440. FOR US SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. If necessary, use CARD D of the P1_LIFESTYLE reference card for him/her to review and provide the appropriate response. A participant must select 'Yes' to at least one option.

The coordinator should make every effort to identify the type of insurance the participant has before selecting the 'Other' option. For example if the participant has Blue Cross/Blue Shield, determine with the participant whether they have an HMO version of the Blue Cross or not. If the insurance plan is a standard Blue Cross that is not an HMO, select 'Yes' for Q1370 and if they indicate the Blue Cross plan is an HMO select 'Yes' for Q1380.

If Q1440 is answered 'Yes', please write the name of the insurance on the descriptive line provided.

Questions 1450 and 1460. FOR CANADIAN SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. The participant must select one of these options.

Question 1470. If the response to Q1470 is 'Yes', complete question 1480.

Questions 1510 and 1520: These questions address whether or not the participant can afford health care vistis and prescriptions. This section is not asking about medication or visit adherence.

Questions 1520 and 1530. Must be completed by the Research Coordinator regarding where the CRF was completed and who completed the CRF.

Questions 1540 – 1560. Q1540 asks if the Research Coordinator reviewed the CRF during the in-person visit, if the form was participant completed. If Q1540 is answered 'Yes', the Research Coordinator must sign and date the form in Q1550 and Q1560.

For more specific details pertaining to smoking history, alcohol use history, recreational drug use history, and health insurance, see LIFESTYLE in Section 1.

2.2.7 Adult Lifestyle 3M (P1_LIFESTYLE_3M)

Purpose: This form collects information on the adult participant's history of smoking, alcohol use, recreational drug use, and current health insurance during the three-month visit only.

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visit 3M

Form Instructions:

Complete the Visit Date as the current date the Adult Lifestyle (P1_LIFESTYLE_3M) form is completed.

Prior to the study visit, the Research Coordinator should complete the date of the last study visit in the shaded box.

If the Research Coordinator completes this questionnaire as an interview with the participant, the participant is reminded of the date of the last ASSESS-AKI Study Visit frequently to keep the participant focused on the covered time period.

If the situations warrants, please refer the participant to the P1_LIFESTYLE reference cards to complete this form.

Question 1000. If the response to Q1000 is 'Yes', complete questions 1010 – 1040.

Question 1030. Round this value to the nearest tenth of a decimal.

Question 1040. If the response is unknown, enter 98 for the value.

Question 1050. If the response to Q1050 is 'Yes', complete questions 1060 – 1090.

Questions 1080/1090. If the participant smokes cigars, but does not smoke daily and does not know how to answer these questions, please leave Q1080 and Q1090 missing in the database. Please note the amount/frequency of cigar smoking as reported by the participant in Q6000. The entry errors for the missing values will need to mark as unresolvable.

Question 1080. Round this value to the nearest tenth of a decimal.

Question 1090. If the response is unknown, enter 98 for the value.

Question 1100. The term regularly means at least two pipefuls of tobacco a week, almost every week. If the response to Q1100 is 'Yes', complete questions 1110 – 1120.

Question 1120. If the response to Q1120 is 'Yes', complete questions 1130 – 1140.

Question 1130. Round this value to the nearest tenth of a decimal.

Question 1140. If the response to Q1140 is 'Yes', complete questions 1150 – 1160. If the response is less than 1 day, record and enter 00 for the value.

Question 1150. Round this value to the nearest tenth of a decimal.

Question 1160. If the response is less than 1 day, record and enter 00 for the value.

Question 1170. If the response to Q1170 is 'Yes', complete questions 1180 – 1220.

Question 1180. If necessary, use CARD A of the P1_LIFESTYLE reference card for him/her to review and provide the appropriate response.

Questions 1190 and 1200. If necessary, use CARD B of the P1_LIFESTYLE reference card for him/her to review and provide the appropriate response.

Question 1210. FOR MEN ONLY. If necessary, use CARD C of the P1_LIFESTYLE reference card for him to review and provide the appropriate response. The participant must select only one response.

Question 1220. FOR WOMEN ONLY. If necessary, use CARD C of the P1_LIFESTYLE reference card for her to review and provide the appropriate response. The participant must select only one response.

Question 1230. If the response to Q1230 is 'Yes', complete question 1240.

Question 1250. If the response to Q1250 is 'Yes', complete question 1260.

Question 1270. If the response to Q1270 is 'Yes', complete question 1280.

Question 1290. If the response to Q1290 is 'Yes', complete question 1300.

Question 1310. If Research Coordinator completed, and Q1310 is 'Yes', have the participant specify the other street drugs and record this in the space provided. If the response to Q1310 is 'Yes', complete question 1320.

Question 1330. If the response to Q1330 is 'Yes', complete questions 1340 – 1440 for the US sites and complete questions 1450-1460 for the Canadian sites.

Questions 1340 - 1440. FOR US SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. If necessary, use CARD D of the P1_LIFESTYLE reference card for him/her to review and provide the appropriate response. A participant must select 'Yes' to at least on option.

The coordinator should make every effort to identify the type of insurance the participant has before selecting the 'Other' option. For example if the participant has Blue Cross/Blue Shield, determine with the participant whether they have an HMO version of the Blue Cross or not. If the insurance plan is a standard Blue Cross that is not an HMO, select 'Yes' for Q1370 and if they indicate the Blue Cross plan is an HMO select 'Yes' for Q1380.

If Q1440 is answered 'Yes', please write the name of the insurance on the descriptive line provided.

Questions 1450 and 1460. FOR CANADIAN SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. The participant must select one of these options.

Question 1470. If the response to Q1470 is 'Yes', complete question 1480.

Questions 1500 and 1510: These questions address whether or not the participant can afford health care vistis and prescriptions. This section is not asking about medication or visit adherence.
Questions 1520 and 1530. Must be completed by the Research Coordinator regarding where the CRF was completed and who completed the CRF.

Questions 1540 – 1560. Q1540 asks if the Research Coordinator reviewed the CRF during the in-person visit, if the form was participant completed. If Q1540 is answered 'Yes', the Research Coordinator must sign and date the form in Q1550 and Q1560.

For more specific details pertaining to smoking history, alcohol use history, recreational drug use history, and health insurance, see LIFESTYLE in Section 1.

2.2.8 Adult Medical History (P1_MEDHX)

Purpose: This form collects the adult participant's history related to cancer treatments, women's health, renal, hypertension, cholesterol, diabetes, and other conditions relevant to the ASSESS-AKI study.

Who: An ASSESS-AKI Research Coordinator interviews the participant to complete the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M.

Form Instructions:

Complete the Visit Date as the current date the Adult Medical History (P1_MEDHX) form is completed.

Prior to the phone call or visit, the Research Coordinator should complete the date of the last study contact in the shaded box. Participants should be instructed to use their best judgment or estimate when answering each question and in the event he/she is unsure, 'Don't know' may be selected.

Question 1000. The participant should respond regarding the diagnosis or treatment by a doctor or other health professional for cancer (excluding non-melanoma skin cancer) since the last ASSESS-AKI study visit. If Q1000 is answered 'Yes', indicate if the participant has received chemotherapy.

Question 1010. If chemotherapy was received, indicate a response for each type the participant received.

Questions 1070 – 1120. These questions refer to the diagnosis or treatment by a doctor or other health professional for the listed conditions since the last ASSESS-AKI study visit. Indicate a response for each condition listed.

Questions 1130 – 1175. FOR FEMALE PARTICIPANTS ONLY. Male participants will proceed to Renal History section.

Question 1130. If the participant has not been pregnant since the last ASSESS-AKI study visit, proceed to Question 1150.

AT V3M ONLY, Question 4 and 4B should be answered based on the time period before enrollment in the study and the current visit date.

Question 1140. If the participant reports she is pregnant at Visit 3M, the subject should be withdrawn from the ASSESS-AKI study.

Questions 1150 – 1175. These questions establish if the female is postmenopausal or has had a hysterectomy. A participant is post-menopausal if she has had no menstrual period for one year.

AT V3M ONLY, Q1150 and Q1175 should be answered based on the time period before enrollment in the study and current visit date.

Question 1150. Ask if she has completed menopause prior to this visit AND enrollment in the study. The window is not limited to the period of time from the index hospitalization to Visit 3M.

Questions 1160-1172. If the participant indicates she is aware of the date for her last menstrual period, complete Question 1170 and 1172.

Questions 1170-1172 If the participant indicates she is aware of the date for her last menstrual period, complete Questions 1170 and 1172.

Prompt the participant to estimate the year her last menstrual period started in Question 1172. The month (Q1170) can be left missing and the error marked unresolvable. If the participant cannot remember either the month or year, Question 1160 should be answered 'No'.

Question 1175. Ask if she had a hysterectomy prior to this visit AND enrollment in the study. The window is not limited to the period of time from index hospitalization to V3M.

Questions 1180 – 1190. These questions refer to medical visits for kidney problems (nephrologist/kidney doctor, or any other physician or health professional) since the last ASSESS-AKI visit. If the response is 'No' to both of these questions, proceed to the vaccine history Question 1230.

Questions 1230 – 1250. If Question 1230 is answered 'Yes', complete Questions 1240 and 1250 regarding what type of vaccinations were given.

Questions 1260 – 1270. Record how long it has been since the participant had his/her blood pressure taken by a doctor or health professional in months, weeks, or days. If the participant does not know, record 98 in Question 1260 and N/A in Question 1270.

Note: The last blood pressure measurement could have occurred at the ASSESS-AKI study visit.

Questions 1280 – 1290. If the participant was diagnosed with hypertension or high blood pressure for the first time (Question 1280 is answered 'Yes'), complete Question 1290 regarding prescribed medication for his/her hypertension or high blood pressure. After Visit 3M, the Research Coordinator should check the P1_MEDHX form(s) at previous visits to verify the participant's response is valid at this visit.

Questions 1300 – 1330. These questions refer to the participant's history of high cholesterol.

Questions 1300 – 1310. Record how long it has been since the participant had his/her blood cholesterol taken by a doctor or health professional in months, weeks, or days. If the participant does not know, record 98 in Question 1300 and N/A in Question 1310.

If the participant indicates he/she has never had his/her blood cholesterol checked, leave Q1300 and Q1310 missing. Enter a comment in Q6000 indicating why the fields were left missing. The entry errors created by the missing values will need to be marked unresolvable.

Questions 1320 – 1330. If the participant was diagnosed with a high blood cholesterol level for the first time (Question 1320 is answered 'Yes'), complete Question 1330 regarding prescribed medication for his/her high blood cholesterol. After Visit 3M, the Research Coordinator should check the P1_MEDHX form(s) at previous visits to verify the participant's response is valid at this visit.

Question 1335. Has the participant ever been told (except during pregnancy) that they have diabetes or high blood sugar? If NO, stop completion of the form. If YES, continue to Q1340,

Question 1340. Since the last ASSESS AKI visit, was the participant diagnosed with diabetes or high blood sugar (except during pregnancy) for the first time. After Visit 3M, the Research Coordinator should check the P1_MEDHX form(s) at previous visits to verify the participant's response is valid at this visit.

Questions 1350 – 1370. Complete these questions based on what the participant is currently doing.

Questions 1380 – 1395. If the participant had his/her eyes examined by a doctor since the last ASSESS AKI visit (Question 1380 is answered 'Yes'), record the month and year of the examination in Q1390 and 1395.

Questions 1410 – 1440. These questions refer to potential problems indicative of diabetic neuropathy that the participant is currently experiencing.

Questions 1450 and 1460. Must be completed by the Research Coordinator regarding where the CRF was completed and who completed the CRF.

Questions 1470 – 1490. Q1470 asks if the Research Coordinator reviewed the CRF during the in-person visit, if the form was participant completed. If Q1470 is answered 'Yes', the Research Coordinator must sign and date the form in Q1480 and Q1490.

2.2.9 Adult Outpatient Demographic Information (P1_OUTPT_DEMO)

Purpose: This form collects outpatient demographic information on the participant's living arrangements, employment, healthcare, and income at the 3-month visit.

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visit 3M

Form Instructions:

Complete the Visit Date as the current date the Adult Outpatient Demographics Information (P1_OUTPT_DEMO) form is completed.

If interview completed, please refer the participant to the P1_OUTPT_DEMO_REF cards to complete this form for questions 1030, 1060, and1070.

Question 1030. During data entry, only one response may be entered in the database. Remind the participant to ONLY select his/her primary employment status. Primary employment status is defined as the employment type that represents greater than 50% of the person's professional activities during the past year. If he/she is in school as well as employed full time, instruct him/her to select his/her desired choice.

If the participant is on temporary medical leave, proceed to Q1060.

If the participant is a high school student, post high school student, has never worked, or he/she doesn't wish to answer, proceed to Q1070. Otherwise, if the participant has worked, complete questions 1040-1060.

Questions 1040 and 1050. If the participant is unsure of his/her last date of employment, explain to him/her to give a best estimate as to when he/she was last employed. The responses to Q1040 and Q1050 should make a partial date in the format of MM/YYYY. If the requested month and/or year is unknown of last employed, coordinators will use 98 for month and 9898 for year.

Questions 1080 and 1090. Must be completed by the Research Coordinator regarding where the CRF was completed and who completed the CRF.

Questions 1100 – 1120. Q1100 asks if the Research Coordinator reviewed the CRF during the in-person visit, if the form was participant completed. If Q1100 is answered 'Yes', the Research Coordinator must sign and date the form in Q1110 and Q1120.

For more specific details pertaining to completion of the form, see Demographics in Section 1.

2.3 PEDIATRIC PROTOCOL SPECIFIC DATA COLLECTION FORMS

Pediatric protocol specific data collection forms are located on the ASSESS-AKI secure website. Individual forms are posted in alphabetical order by form code in the Individual Forms folder.

When preparing for a visit, the Research Coordinator will print a complete visit packet from a center specific folder located in Protocols:Forms:Pediatric(P2): Visit Packets. Each visit packet will begin with a data processing cover sheet, followed by the visit procedure checklist, and each form (standard or protocol specific) to be used during the visit.

Visit packets posted on the website have been programmed to allow header information to be pre-filled on each page prior to printing the packet. Using the pre-fill option will ensure each page identifies a participant ID in the event forms become dislodged from the packet.

2.3.1 PedsQL™ Child Report (Ages 8-12) (PDQLCR812)

Purpose: This form records quality of life measures regarding health and activities, feelings, getting along with others, and school for children at the age of 8-12.

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Refer to the Quality of Life and Cognitive Function Manual for detailed instructions on preparation and administration of the questionnaire.

2.3.2 PedsQL™ Parent Report for Young Children (Ages 2 – 4) (PDQLPR24)

Purpose: This form records quality of life measures regarding physical functioning, emotional functioning, social functioning, and school functioning for children at the age of 2-4.

Who: An ASSESS-AKI Research Coordinator or guardian completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Refer to the Quality of Life and Cognitive Function Manual for detailed instructions on preparation and administration of the questionnaire.

2.3.3 PedsQL™ Parent Report for Young Children (Ages 5 – 7) (PDQLPR57)

Purpose: This form records quality of life measures regarding physical functioning, emotional functioning, social functioning, and school functioning for children at the age of 5-7.

Who: An ASSESS-AKI Research Coordinator or guardian completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Refer to the Quality of Life and Cognitive Function Manual for detailed instructions on preparation and administration of the questionnaire.

2.3.4 PedsQL™ Parent Report for Children (Ages 8 – 12) (PDQLPR812)

Purpose: This form records quality of life measures regarding physical functioning, emotional functioning, social functioning, and school functioning for children at the age of 8-12.

Who: An ASSESS-AKI Research Coordinator or guardian completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Refer to the Quality of Life and Cognitive Function Manual for detailed instructions on preparation and administration of the questionnaire.

2.3.5 PedsQL™ Parent Report for Teens (Ages 13 - <18) (PDQLPR1318)

Purpose: This form records quality of life measures regarding physical functioning, emotional functioning, social functioning, and school functioning for children at the age of 13-<18.

Who: An ASSESS-AKI Research Coordinator or guardian completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Refer to the Quality of Life and Cognitive Function Manual for detailed instructions on preparation and administration of the questionnaire.

2.3.6 PedsQL™ Teen Report (Ages 13 - <18) (PDQLTR1318)

Purpose: This form records quality of life measures regarding health and activities, feelings, getting along with others, and school for children at the age of 13-<18.

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Refer to the Quality of Life and Cognitive Function Manual for detailed instructions on preparation and administration of the questionnaire.

2.3.7 PedsQL™ Young Adult Report (Ages 18 – 25) (PDQLYAR1825)

Purpose: This form records quality of life measures regarding health and activities, feelings, getting along with others, and school for children at the age of 18-25.

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Refer to the Quality of Life and Cognitive Function Manual for detailed instructions on preparation and administration of the questionnaire.

2.3.8 PedsQL™ Young Child Report (Ages 5 – 7) (PDQLYCR57)

Purpose: This form records quality of life measures regarding physical functioning, emotional functioning, social functioning, and school functioning for children at the age of 5-7.

Who: An ASSESS-AKI Research Coordinator or guardian completes the form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Refer to the Quality of Life and Cognitive Function Manual for detailed instructions on preparation and administration of the questionnaire.2.3.9 Pediatric Alert (P2_ALERT)

Purpose: This form for the pediatric participant identifies potential serious medical problem(s) such as changes in blood pressure, acute distress symptoms, or changes in laboratory results of interest to the ASSESS-AKI study.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 3M - 90M, as necessary upon identification of alert information associated with ASSESS study visits and tests.

Form Instructions:

Complete the Visit Date as the current date the Pediatric Alert (P2_ALERT) form is completed.

If the alerts happen on different days, multiple P2_ALERT forms would be used. For example, there would be multiple alert forms completed related to an elevated BP reading and an out-of-range lab value. The BP value would be recorded on the visit date when the blood pressure reading is taken and recorded and the coordinator notes the value is out-of-range. The lab value would be recorded on the date that the results are received from the lab and an out-of- range value is reported.

If more than one alert happens on the same day, those alerts would be recorded on one P2_ALERT form, For example, an elevated blood pressure reading is noted, and the participant also has symptoms of acute distress. Both of these are noted in the clinic on the day of the visit and would be recorded on one P2_ALERT form.

Question 1000. The date of the alert could be the date of the ASSESS study visit or when the laboratory report is received. For example, if a laboratory value indicates an alert, use the date the laboratory report was received as the Date of Alert Value(s).

Prior to December 14, 2012:

Question 1010. Use the Height and Gender Blood Pressure Norms Chart (P2_BLOOD_PRESSURE_TABLE_CHILD, BP_REF_INFANTS) reference cards to identify if the alert is due to Stage 2 hypertension (> 95th percentile). The reference charts are posted on the ASSESS website.

After December 14, 2012:

Question 1010. Use the Height and Gender Blood Pressure Norms Chart (P2_BLOOD_PRESSURE_TABLE_CHILD, BP_REF_INFANTS) reference cards to identify if the alert is due to Stage 2 hypertension. This is defined as greater than the 99th percentile plus 5mmHg. The reference charts are posted on the ASSESS website.

For Pediatric participants > 17 years of age, the systolic blood pressure is >140mmHg; diastolic blood pressure is > 90mmHg.

Question 1020. If the alert was due to hypotension, indicate the criterion that was met in Q1030 or Q1040.

Question 1030. The 'N/A' option should be selected for pediatric participants that are older than 1 year.

Question 1040. The 'N/A' option should be selected for pediatric participants that are younger than 1 year of age.

Question 1050. If the alert is due to acute distress, complete Q1060 – Q1090. If No, proceed to Q1100.

Questions 1060-1090. Acute distress is identified by three items – chest pain, severe respiratory distress, and acute neurological symptoms. Other symptoms determined as acute by the Principal Investigator or the Research Coordinator are noted under 'Other' category and specified in the space provided.

Question 1100. If the alert is due to laboratory results, answer 'Yes' to Q1100 and complete Q1140 and Q1160. If No, proceed to Q1170.

Questions 1140-1160. Laboratory results identified as outside the range listed on the Pediatric Alert (P2_ALERT) form will be checked 'Yes', and all values within the range are checked 'No'.

Question 1140. For the outpatient annual visits, the value from the Central Lab of the previous ASSESS visit is used to determine a doubling of the serum creatinine. Montreal uses the local serum creatinine for the V0 vs. V3M comparisons.

Question 1160. Laboratory results, other than those listed on the data collection form, determined as abnormal are noted as 'Other' and identified in the space provided.

Question 1170. Indicate if the Research Coordinator notified the Principal Investigator of the alert(s).

Question 1180. Indicate the action taken following the review of alert(s). If 'Other' is selected, a description should be provided on the form.

Question 1190. Indicate if the participant or parent/guardian was made aware of the medical alert. It is the responsibility of the Research Coordinator and/or the Principal Investigator to decide when/if to inform the participant or parent/guardian of the outcome.

2.3.10 Pediatric Medical Events Questionnaire (P2_EVENTS)

Purpose: This form for the pediatric participant collects information about the frequency of hospitalizations/ER visits, number of heart surgeries, type of heart surgeries; admission to intensive care units (ICU), reasons for admission to ICU, type of test/procedures performed, and documents the death of a participant.

Who: An ASSESS-AKI Research Coordinator completes the form as an interview.

When: Visits 3M-90M

Form Instructions:

Complete the visit date as the current date the Pediatric Event Questionnaire (P2_EVENTS) form is completed.

If the P2_EVENTS form is completed outside of the in person visit or phone contact use the visit number closest to the time the event is reported. If the participant has missed a visit or phone contact, these packets will need to be marked missing before the single P2_EVENTS form is entered.

For example, if an event is reported and the last visit completed was V12M and the event occurred near the 36M visit, the V18M, V24M, and V30M visits will need to be set to missing in the database before the V36M P2_EVENTS form can be data entered.

The Research Coordinator completes this questionnaire as an interview with the participant or the participant's parent/guardian. Prior to the phone call or visit, the Research Coordinator should complete the date of the last study contact in the shaded box. This date will help the participant or parent/guardian focus on the time between the last study contact and the current study contact.

If the participant or parent/guardian is unsure if an event was previously reported at a study contact, the Research Coordinator should record the event and confirm the event through review of medical records and past Event Information Sheets (EVENT_INFO) forms.

Questions 1000-1120. If 'Yes' is checked for a hospitalization or emergency room visit for any medical problems in Q1000, each subsequent item requires a 'Yes' or 'No' response, and the number of hospitalizations or ER visits per event. Admission to an inpatient rehabilitation unit or drug/alcohol treatment facility is not considered to be a hospitalization.

If 'No' is checked in response to Q1000, proceed to Question 1140.

Questions 1110-1120 If the medical condition/problem does not fit into any of the listed categories in Q1010 – Q1100, check Q1110 for 'other' and list the number of ER visits/hospitalizations that fall under this category.

Question 1130. The Research Coordinator determines the number of separate hospitalizations, based on the 'Yes' responses by the participant/participant's guardian and review of medical records.

Note: Some conditions may have occurred during the same hospitalization.

The Research Coordinator must complete the Event information Sheet (EVENT_INFO) form and Hospital/ER Record Evaluation (HOSP_EVAL) form for each separate hospitalization/ER visit except when death occurs outside of the hospital and is reported by proxy.

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Beginning on April 11, 2013

Exceptions: If the ER visit lasts <23 hours and did not required admission, a HOSP_EVAL form should not be completed. If a hospitalization lasts <23 hours, a HOSP_EVAL form should not be completed. If an event meets either of these two criteria, this information may be entered into Q6000 on the P2_EVENTS form (if the form is still present at the center) or documented in the participant study file for reference to any queries sent by the DCC.

Questions 1140-1200. If 'Yes' is checked for heart surgery since the last ASSESS-AKI study contact, the Research Coordinator should ask the participant about each procedure in Q1160 – Q1200.

Question 1210. If other surgical procedures is marked as 'Yes', list the procedure on the line to the right. The textual response will not be entered into the study database.

If 'No' is checked in response to Q1140, proceed to Question 1220.

Questions 1220-1260. If 'Yes' is checked for admission to the intensive care unit since the last ASSESS-AKI study contact in Q1220, the Research Coordinator should complete Q1230 – Q1260.

If 'No' is checked in response to Q1220, proceed to Question 1280.

Questions 1280-1290. If the surgery type listed was performed, indicate the setting where the surgery was performed in Q1290.

Question 1300. The Research Coordinator determines the number of separate tests or procedures completed, based on the 'Yes' responses by the participant in Q1280 and the review of medical records.

The Research Coordinator must complete an Event Information Sheet (EVENT_INFO) form for each test or procedure performed. In addition, a Hospital/ER Record Evaluation (HOSP_EVAL) form *may* be completed for inpatient settings. During review of medicals records, if the coordinator finds the test/procedure is already documented on a HOSP_EVAL form in response to Question 1, a separate HOSP_EVAL form is not required. An Outpatient Vascular Procedure Evaluation (OUTPT_VASC) form for outpatient settings.

Questions 1320-1330. If the treatment type listed was performed, indicate the setting where the treatment was performed in Q1330.

Question 1340. The Research Coordinator determines the number of treatments completed, based on the 'Yes' response by the participant in Q1320 and the review of medical records.

For participants who answer Yes to Q1320 on the Pediatric Medical Event Questionnaire (P2_EVENTS) as having received dialysis, a course of dialysis (having a start/stop date) is counted as one when answering

Q1320 on the Pediatric Medical Event Questionnaire (P2_EVENTS). Each day of the dialysis should not be counted; it is the number of dialysis courses that should be counted.

The Research Coordinator must complete an Event Information Sheet (EVENT_INFO) form for each treatment. In addition the Hospital/ER Record Evaluation (HOSP_EVAL)
Form *may* be completed for inpatient settings. During review of medicals records, if the coordinator finds the test/procedure is already documented on a HOSP_EVAL form in response to Question 1, a separate HOSP_EVAL form is not required. A Dialysis Evaluation (DIAL_EVAL) form for outpatient settings. Dialysis in an inpatient rehabilitation unit should be considered as outpatient.

Questions 1350-1360. If death is reported, indicate the name of the informant in the space provided and the date of death.

If the death occurred during an ER visit lasting less than 23hrs, a HOSP_EVAL form should be completed.

If death is reported, the Research Coordinator must complete the ASSESS-AKI Withdrawal (WITHDR) form and the Death Record Evaluation (DEATH_EVAL) form.

2.3.11 Pediatric Inpatient Checklist 1 (P2_INPATIENT1)

Purpose: This form records the pediatric participant's past medical history, smoking history, renal medical history, baseline creatinine value, and pre-admission medication use. The information will be collected using chart review and participant self-report.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visit 0

Form Instructions:

Complete the Visit Date as the current date the Pediatric Inpatient Checklist 1 (P2_INPATIENT1) form is completed.

Note: This may not necessarily be the date the checklist was initiated. If the information remains unknown after a chart review and participant interview, mark 'Unknown' if that response is available.

Question 1000. If the response to Q1000 is 'Yes', complete question 1010.

Question 1080. If the response to Q1080 is 'Yes', complete question 1090.

Question 1090. Round the value to the nearest number of whole weeks.

Question 1120. If the response to Q1120 is 'Yes', complete questions 1130 and 1140.

Question 1140. Record the date of the participant's last heart surgery. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

If the site is unable to find the date in the medical record, and the participant or parent/guardian can provide the year that it occurred, the coordinator should use 01/01/YYYY. 'YYYY' should be the year that was provided by the participant or parent/guardian. If unknown, leave the value missing and mark the error as unresolvable.

Question 1150. If the response to Q1150 is 'Yes', complete question 1160.

Question 1170. If the response to Q1170 is 'Yes', complete question 1180.

Questions 1190-1210. Check 'Yes' or 'No' to each response.

Question 1220. This value should be obtained from the BASE_CREATININE form.
If a participant has more than one available outpatient, non-emergency department test result the most recent value prior to hospitalization should be considered the baseline.
Round the value to the nearest ten hundredths decimal place.

Question 1230. The unit mg/dL has been designated as the accepted measurement for the United States sites and umol/L has been designated as the accepted measurement for the Canadian sites.

Question 1240. Do not complete this question for control participants. The date of AKI episode should correspond to the peak inpatient creatinine value recorded on the INPT_CREATININE form.

For more specific details pertaining to past medical history and renal medical history, see Medical History in Section 1.

2.3.12 Pediatric Inpatient Checklist 2 (P2_INPATIENT2)

Purpose: This form evaluates the pediatric participant's medications given during hospitalization, in hospital exposures and complications, dialysis, ICU, and length of hospital stay.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: After the participant is discharged from the hospital (Visit 0)

Form Instructions:

Complete the Visit Date as the current date the Pediatric Inpatient Checklist 2 (P2_INPATIENT2) form is completed.

Note: This may not necessarily be the date the checklist was initiated. If the information remains unknown after a chart review and participant interview, mark 'Unknown' if that response is available.

Questions 1000-1070. Complete these questions at or after discharge based on any medications given anytime during the entire hospitalization.

Question 1080. If the response to Q1080 is 'Yes', complete questions 1090 - 1100.

Questions 1110 and 1140. Complete this question for CASE participants only.

Question 1130. Complete 'Yes' if the participant returned to the OR after the original surgery.

Question 1140. If the response to Q1140 is 'Yes', complete questions 1150 - 1180.

Question 1180. If the response to Q1180 is 'Yes', please specify the other surgical procedure.

Question 1240. If the response to Q1240 is 'Yes', complete questions 1250 - 1320.

Questions 1250-1260, 1310-1320, and 1340-1350. During data entry, the '/'s can either be entered or left missing, as long as a full date is entered. Example: 01012009 or 01/01/2009 are both acceptable but 112009 or 010109 are incorrect.

Question 1260. Stop date for last dialysis will remain missing if participant discharged from the hospital requiring dialysis treatment.

Question 1330. A 24-hour period is equal to 1 day, except if the last day is < 24 hours, than count that last day as 1 day.

For more specific details pertaining to medications, in hospital exposures/complications or physiological data, see Medical History and Visit Zero in Section 1.

2.3.13 Pediatric Inpatient Demographic Information (P2_INPT_DEMO)

Purpose: This form collects inpatient demographic information on the pediatric participant's living arrangements, employment, healthcare, and income at the index hospitalization as well as the participant's guardian(s).

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visit 0

Form Instructions:

Complete the Visit Date as the current date the Pediatric Demographics Information (P2_INPT_DEMO) form is completed.

If the situations warrants, please refer the participant to the P2_INPT _DEMO_REF cards to complete this form.

Question 1000. If the response to Q1000 is 'No', complete questions 1010 - 1020.

Questions 1010 and 1020. Advise the participant to estimate if uncertain.

Question 1040. If the response to Q1040 is 'Yes', complete questions 1050 - 1060.

Questions 1100 - 1200. FOR US SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. If necessary, use CARD D of the P2_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response. A participant must select 'Yes' to at least one option.

The coordinator should make every effort to identify the type of insurance the participant has before selecting the 'Other' option. For example if the participant has Blue Cross/Blue Shield, determine with the participant whether they have an HMO version of the Blue Cross or not. If the insurance plan is a standard Blue Cross that is not an HMO, select 'Yes' for Q1130 and if they indicate the Blue Cross plan is an HMO select 'Yes' for Q1140.

If Q1200 is answered 'Yes', please write the name of the insurance on the descriptive line provided.

Questions 1210 and 1220. FOR CANADIAN SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. The participant must select one of these options.

Question 1230. If necessary, use CARD E of the P2_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response.

Question 1240. If the response to Q1090 is 'Zero', STOP and do not complete the rest of the form.

Question 1270. If necessary, use CARD A of the P2_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response.

Question 1280. During data entry, only one response can be captured in the database. Remind the participant to ONLY select his/her primary employment status. Primary employment status is defined as the

employment type that represents greater than 50% of the person's professional activities during the past year. If he/she is in school as well as employed full time, instruct him/her to select his/her desired choice. If necessary, use CARD B of the P2_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response.
If the guardian is on temporary medical leave, proceed to Q1310.

If the guardian is a student, has never worked, or he/she doesn't wish to answer proceed to Q1320. Otherwise if the guardian has worked, complete questions 1290-1310. If there is only one guardian who has never worked or don't wish to answer, do not complete the rest of the form.

Questions 1290-1300. If participant is unsure of his/her last date of employment, explain to him/her to give a best estimate as to when he/she was last employed. The responses to Q1290/Q1300 should make a partial date in the format of MM/YYYY. If the requested month and/or year is unknown of last employed, coordinators will use 98 for month and 9898 for year.

Question 1310. If necessary, use CARD C of the P2_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response.

Question 1340. If necessary, use CARD A of the P2_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response.

Question 1350. During data entry, only one response can be captured in the database, therefore please remind the participant to ONLY select his/her primary employment status. Primary employment status is defined as the employment type that represents greater than 50% of the person's professional activities during the past year. If he/she is in school as well as employed full time, instruct him/her to select his/her desired choice. If necessary, use CARD B of the P2_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response.

If the guardian is on temporary medical leave, proceed to question 1380.

If the guardian is a student, has never worked, or he/she doesn't wish to answer STOP. Otherwise if the guardian has worked, complete questions 1360-1380.

Questions 1360-1370. If participant is unsure of his/her last date of employment, explain to him/her to give a best estimate as to when he/she was last employed. The responses to and Q1360/Q1370 should make a partial date in the format of MM/YYYY. If the requested month and/or year is unknown of last employed, coordinators will use 98 for month and 9898 for year.

Question 1380. If necessary, use CARD C of the P2_INPT_DEMO_REF reference card for him/her to review and provide the appropriate response.

For more specific details pertaining to completion of the form, see Demographics in Section 1.

2.3.14 Pediatric Lifestyle (P2_LIFESTYLE)

Purpose: This form collects information on the pediatric participant's current education status, history of smoking, alcohol use, recreational drug use, and health insurance during the yearly in-person visits.

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visits 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Complete the Visit Date as the current date the Pediatric Lifestyle (P2_LIFESTYLE) form is completed.

Prior to the study visit, the Research Coordinator should complete the date of the last study visit in the shaded box.

If the Research Coordinator completes this questionnaire as an interview with the participant or guardian, the participant/guardian is reminded of the date of the last ASSESS-AKI Clinic Visit frequently to keep the participant focused on the covered time period.
If the situations warrants, please refer the participant to the P2_LIFESTYLE reference cards to complete this form.

Question 1000. Record 'Yes' if the participant is in grades K-12. If the response to Q1000 is 'Yes', complete questions 1010 – 1030. If the response to Q1000 is no, record the explanation in the space below.

Question 1010. If the participant is between grades, enter the last grade completed.

Question 1020. If the child is receiving any form of special education a description should be provided on the form. This response will not be entered into the study database.

Questions 1040-1360. Complete these responses only if the participant is greater than or equal to 12 years of age.

Question 1040. If the response to Q1040 is 'Yes', complete questions 1050-1100.

Question 1050. If the response to Q1050 is greater than 1, complete questions 1060.

Question 1090. Round this value to the nearest tenth of a decimal.

Question 1100. If the participant is unsure of the amount, record and enter 98 for the value.

Question 1110. If the response to Q1110 is 'Yes', complete questions 1120 – 1150.

Questions 1140/1150. If the participant smokes cigars, but does not smoke daily and does not know how to answer these questions, please leave Q1140 and Q1150 missing in the database. Please note the amount/frequency of cigar smoking as reported by the participant in Q6000. The entry errors for the missing values will need to marked as unresolvable.

Question 1140. Round this value to the nearest tenth of a decimal.

Question 1150. If the participant is unsure of the amount, record and enter 98 for the value.

Question 1160. The term regularly means at least two pipefuls of tobacco a week, almost every week. If the response to Q1160 is 'Yes', complete questions 1190 and 1220.

Question 1190. Round this value to the nearest tenth of a decimal.

Question 1200. If the response is less than 1 pipeful per day, record and enter 00 for the value. Proceed to Q1230.

Question 1230. If the response to Q1230 is 'Yes', complete questions 1240 - 1260.

Question 1240. If necessary, use CARD A of the P2_LIFESTYLE reference card for him/her to review and provide the appropriate response.

Question 1250 and 1260. If necessary, use CARD B of the P2_LIFESTYLE reference card for him/her to review and provide the appropriate response.

Question 1270. If the response to Q1270 is 'Yes', complete question 1280.

Question 1290. If the response to Q1290 is 'Yes', complete question 1300.

Question 1310. If the response to Q1310 is 'Yes', complete question 1320.

Question 1330. If the response to Q1330 is 'Yes', complete question 1340.

Question 1350. If Research Coordinator completed, and Q1350 is 'Yes', have the participant specify the other street drugs and record this in the space provided. If Q1350 is answered 'Yes', complete question 1360.

Question 1370. If the response to Q1370 is 'Yes', complete questions 1340 - 1530.

Questions 1380 - 1480. FOR US SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. If necessary, use CARD D of the P2_LIFESTYLE reference card for him/her to review and provide the appropriate response. A participant must select 'Yes' to at least on option.

The coordinator should make every effort to identify the type of insurance the participant has before selecting the 'Other' option. For example if the participant has Blue Cross/Blue Shield, determine with the participant whether they have an HMO version of the Blue Cross or not. If the insurance plan is a standard Blue Cross that is not an HMO, select 'Yes' for Q1410 and if they indicate the Blue Cross plan is an HMO select 'Yes' for Q1420.

If Q1480 is answered 'Yes', please write the name of the insurance on the descriptive line provided.

Questions 1490 and 1500. FOR CANADIAN SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. The participant must select one of these options.

Question 1510. If the response to Q1510 is 'Yes', complete question 1520.

Questions 1560 and 1570. Must be completed by the Research Coordinator regarding where the CRF was completed and who completed the CRF.

Questions 1580 – 1600. Q1580 asks if the Research Coordinator reviewed the CRF during the in-person visit, if the form was participant completed. If Q1580 is answered 'Yes', the Research Coordinator must sign and date the form in Q1590 and Q1600.
For more specific details pertaining to smoking history, alcohol use history, recreational drug use history, and health insurance, see LIFESTYLE in Section 1.

2.3.15 Pediatric Lifestyle (P2_LIFESTYLE_3M)

Purpose: This form collects information on the pediatric participant's education status, history of smoking, alcohol use, recreational drug use, and health insurance during the three-month visit only.

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visit 3M

Form Instructions:

Complete the Visit Date as the current date the Pediatric Lifestyle (P2_LIFESTYLE_3M) form is completed.

Prior to the study visit, the Research Coordinator should complete the date of the last study visit in the shaded box.

If the Research Coordinator completes this questionnaire as an interview with the participant or guardian, the participant/guardian is reminded of the date of the last ASSESS-AKI Clinic Visit frequently to keep the participant focused on the covered time period.
If the situations warrants, please refer the participant to the P2_LIFESTYLE reference cards to complete this form.

Question 1000. Record 'Yes' if the participant is in grades K-12. If the response to Q1000 is 'Yes', complete questions 1010 – 1030. If the response to Q1000 is no, record the explanation in the space below.

Question 1010. If the participant is between grades, enter the last grade completed.

Question 1020. If the child is receiving any form of special education a description should be provided on the form. This response will not be entered into the study database.

Questions 1040-1360. Complete these responses only if the participant is greater than or equal to 12 years of age.

Question 1040. If the response to Q1040 is 'Yes', complete questions 1050-1100.

Question 1050. If the response to Q1050 is greater than 1, complete questions 1060.

Question 1090. Round this value to the nearest tenth of a decimal.

Question 1100. If the participant is unsure of the amount, record and enter 98 for the value.

Question 1110. If the response to Q1110 is 'Yes', complete questions 1120 – 1150.

Questions 1140/1150. If the participant smokes cigars, but does not smoke daily and does not know how to answer these questions, please leave Q1140 and Q1150 missing in the database. Please note the amount/frequency of cigar smoking as reported by the participant in Q6000. The entry errors for the missing values will need to be mark as unresolvable.

Question 1140. Round this value to the nearest tenth of a decimal.

Question 1150. If the participant is unsure of the amount, record and enter 98 for the value.

Question 1160. The term regularly means at least two pipefuls of tobacco a week, almost every week. If the response to Q1160 is 'Yes', complete questions 1170 – 1220.

Question 1180. If the response to Q1180 is 'Yes', complete questions 1190 – 1200.

Question 1190. Round this value to the nearest tenth of a decimal.

Question 1200. If the response is less than 1 day, record and enter 00 for the value. Proceed to Q1230.

Question 1210. Round this value to the nearest tenth of a decimal.

Question 1220. If the response is less than 1 day, record and enter 00 for the value.

Question 1230. If the response to Q1230 is 'Yes', complete questions 1240 - 1260.

Question 1240. If necessary, use CARD A of the P2_LIFESTYLE reference card for him/her to review and provide the appropriate response.

Question 1250 and 1260. If necessary, use CARD B of the P2_LIFESTYLE reference card for him/her to review and provide the appropriate response.

Question 1270. If the response to Q1270 is 'Yes', complete question 1280.

Question 1290. If the response to Q1290 is 'Yes', complete question 1300.

Question 1310. If the response to Q1310 is 'Yes', complete question 1320.

Question 1330. If the response to Q1330 is 'Yes', complete question 1340.

Question 1350. If Research Coordinator completed, and Q1350 is 'Yes', have the participant specify the other street drugs and record this in the space provided. If Q1350 is answered 'Yes', complete question 1360.

Question 1370. If the response to Q1370 is 'Yes', complete questions 1340 - 1530.

Questions 1380 - 1480. FOR US SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. If necessary, use CARD D of the P2_LIFESTYLE
reference card for him/her to review and provide the appropriate response. A participant must select 'Yes' to at least on option.
The coordinator should make every effort to identify the type of insurance the participant has before selecting the 'Other' option. For example if the participant has Blue Cross/Blue Shield, determine with the participant whether they have an HMO version of the Blue Cross or not. If the insurance plan is a standard Blue Cross that is not an HMO, select 'Yes' for Q1410 and if they indicate the Blue Cross plan is an HMO select 'Yes' for Q1420.

If Q1480 is answered 'Yes', please write the name of the insurance on the descriptive line provided.

Questions 1490 and 1500. FOR CANADIAN SITES ONLY. Have the participant answer yes or no to each type of healthcare coverage. The participant must select one of these options.

Question 1510. If the response to Q1510 is 'Yes', complete question 1520.

Questions 1560 and 1570. Must be completed by the Research Coordinator regarding where the CRF was completed and who completed the CRF.

Questions 1580 – 1600. Q1580 asks if the Research Coordinator reviewed the CRF during the in-person visit, if the form was participant completed. If Q1580 is answered 'Yes', the Research Coordinator must sign and date the form in Q1590 and Q1600.

For more specific details pertaining to smoking history, alcohol use history, recreational drug use history, and health insurance, see LIFESTYLE in Section 1

2.3.16 Pediatric Medical History (P2_MEDHX)

Purpose: This form collects the pediatric participant's history related to cancer treatments, neurological disease, women's health, renal, hypertension, diabetic, growth and nutrition and other conditions relevant to the ASSESS-AKI study.

Who: The ASSESS-AKI Research Coordinator interviews the participant or parent/guardian to complete this form.

When: Visits 3M, 12M, 24M, 36M, 48M, 60M, 72M, 84M

Form Instructions:

Complete the Visit Date as the current date the Pediatric Medical History (P2_MEDHX) form is completed.

Prior to the visit, the Research Coordinator should complete the date of the last study visit in the shaded box. Participants should be instructed to use his/her best judgment or estimate when answering each question and in the event he/she is unsure, 'Don't know' may be selected.

Question 1000. The participant or parent/guardian should respond regarding the diagnosis or treatment by a doctor or other health professional for cancer (excluding non-melanoma skin cancer) since the last ASSESS-AKI study visit. If 'Yes' indicate if the participant has received chemotherapy.

Question 1010. If chemotherapy was received, indicate a response for each type the participant received.

Questions 1060 – 1310. These questions refer to the diagnosis or treatment by a doctor or other health professional for the listed conditions since the last ASSESS-AKI visit. Indicate a response for each condition listed. If 'Other' is marked 'Yes' for Question 1180 or 1280 , please specify a response in the space provided. Textual responses will not be entered into the study database.

Questions 1320 – 1385. FOR FEMALE PARTICIPANTS ONLY. Male participants will proceed to the Renal History section.

Question 1320. If the participant has not been pregnant since the last ASSESS-AKI study visit, proceed to Question 1340.

Question 1330. If the participant or parent/guardian reports she/the participant is pregnant at Visit 3, the subject should be withdrawn from the ASSESS-AKI study.

AT V3M ONLY, Questions 4, 5, and 6 should be answered based on the time period before enrollment in the study and the V3M visit date.

Questions 1340 – 1355. If the participant, or participant's guardian, indicates awareness of when the participant started menstruation, complete Q1340 as 'Yes'. Q1350 and Q1355 can be completed to document the month and year. If Q1340 is answered 'No' or 'Don't Know', proceed to Q1390.

Questions 1370 – 1385. If the participant or parent/guardian knows when the last menstrual period started, complete Q1370 as 'Yes'. Q1380, Q1382, Q1385 can be completed to document the month, day and year if known.

Prompt the participant/parent/guardian to estimate the year her last menstruation started in Q1385. The month (Q1380) and day (Q1382) can be left missing (if necessary) and the errors marked unresolvable. If the participant cannot remember the month, day, or year, Q1370 should be answered 'No' or 'Don't Know'.

Questions 1390 – 1400. These questions refer to medical visits for kidney problems (nephrologist/kidney doctor, or any other physician or health professional) since the last ASSESS-AKI visit. If the response is 'No' to both of these questions, proceed to vaccine history Question 1550. If the response to either of these questions is 'Yes', complete Q1410 – Q1540 regarding the diagnosis or treatment of the conditions listed.

Questions 1550 – 1590. If Question 1550 is answered 'Yes', vaccinations were given to lower the risk of infection, complete Questions 1560, 1570, and 1580 regarding what type of vaccinations were given. If Question 1580 is answered 'Yes', complete Question 1590 with the number of RSV vaccines the participant received.

Questions 1600 – 1610. Record how long it has been since the participant had his/her blood pressure taken by a doctor or health professional in months, weeks, or days. If the participant does not know, record 98 in Question 1600 and N/A in Question 1610.

Note: The last blood pressure measurement could have occurred at the last ASSESS-AKI study visit.

Questions 1620 – 1630. If the participant was diagnosed with hypertension or high blood pressure for the first time (Question 1620 is answered 'Yes'), complete Question 1630 regarding prescribed medication for his/her hypertension or high blood pressure. If after Visit 3M, the Research Coordinator should check the P2_MEDHX form(s) at previous visits to verify the participant's response is valid at this visit.

Question 1635. Have you/your child ever been told that you/your child have diabetes or high blood sugar? If NO, proceed to Q1750. If YES, continue to Q1640.

Question 1640. Since the last ASSESS AKI visit was the participant diagnosed with diabetes or high blood sugar for the first time. After Visit 3M, the Research Coordinator should check the P2_MEDHX form(s) at previous visits to verify the participant's response is valid at this visit.

Questions 1650 – 1670. Complete these questions based on what the participant is currently doing.

Questions 1680 – 1695. Answer these questions looking at the time period since the last ASSESS AKI visit. If the participant had his/her eyes examined by a doctor (Question 1680 is answered 'Yes'), record the month and year of the examination in Questions 1690 and 1695.

Prompt the participant/parent/guardian to estimate the year the eye examination occurred in Q1695. The month (Q1690) can be left missing and the error marked unresolvable. If the participant or parent/guardian cannot remember either the month or year, Q1680 should be answered 'No' or 'Don't Know'.

Questions 1710 – 1740. These questions refer to potential problems indicative of diabetic neuropathy that the participant is currently experiencing.

Questions 1750 – 1790. If the participant has been diagnosed with a weight, height, or growth abnormality since the last ASSESS-AKI study visit complete Q1760-1790. Otherwise, proceed to Q1800. If you answer 'Yes' to both 1770 and 1780, you should answer 'Yes' to 1790.

Questions 1820 -1850. If the participant has any food restrictions for medical reasons, complete Q1830-Q1850. If 'No', proceed to Q1860

Questions 1860 and 1870. Must be completed by the Research Coordinator regarding where the CRF was completed and who completed the CRF.

Questions 1880 – 1900. Q1880 asks if the Research Coordinator reviewed the CRF during the in-person visit, if the form was participant completed. If Q1880 is answered 'Yes', the Research Coordinator must sign and date the form in Q1890 and Q1900.

For more specific details pertaining to completion of the form, see Medical History in Section 1.

2.3.17 Pediatric Outpatient Demographic Information (P2_OUTPT_DEMO)

Purpose: This form collects outpatient demographic information on the pediatric participant's living arrangements and legal guardian's employment, healthcare, and income at the 3-month visit.

Who: An ASSESS-AKI Research Coordinator or participant/guardian completes the form.

When: Visit 3M

Form Instructions:

Complete the Visit Date as the current date the Pediatric Outpatient Demographics Information (P2_OUTPT_DEMO) form is completed.

Question 1000-1020. If the response to Q1000 is 'No', complete questions 1010 and 1020.

Question 1040-1060. If the response to Q1040 is 'Yes', complete questions 1050 and 1060.

Question 1080. If necessary, use CARD A of the P2_DEMO_REF reference card for him/her to review and provide the appropriate response.

Question 1090. If the response to Q1090 is 'Zero', STOP and do not complete the rest of the form. The research coordinator should complete the shaded box at the end of the form.

Question 1120. If necessary, use CARD B of the P2_DEMO_REF reference card for him/her to review and provide the appropriate response.

Question 1130. During data entry, only one response can be entered in the database, therefore please remind the participant/guardian to ONLY select his/her primary employment status. Primary employment status is defined as the employment type that represents greater than 50% of the person's professional activities during the past year. If he/she is in school as well as employed full time, instruct him/her to select his/her desired choice. If necessary, use CARD C of the P2_DEMO_REF reference card for him/her to review and provide the appropriate response.

If the guardian is on temporary medical leave, proceed to Q1160.

If the guardian is a student, has never worked, or he/she doesn't wish to answer proceed to Q1170 or if there is only one guardian, proceed to Q1240. Otherwise if the guardian has worked, complete questions 1140-1160. The research coordinator should complete the information in the shaded box at the end of the form.

Questions 1140 and 1150. If participant/guardian is unsure of his/her last date of employment, explain to him/her to give a best estimate as to when he/she was last employed. The responses to Q1140 and Q1150 should make a partial date in the format of MM/YYYY. If the requested month and/or year is unknown of last employed, coordinators will use 98 for month and 9898 for year.

Question 1160. If necessary, use CARD D of the P2_DEMO_REF reference card for him/her to review and provide the appropriate response.

Question 1190. If necessary, use CARD B of the P2_DEMO_REF reference card for him/her to review and provide the appropriate response.

Question 1200. During data entry, only one response can be entered in the database, therefore please remind the participant/guardian to ONLY select his/her primary employment status. Primary employment status is defined as the employment type that represents greater than 50% of the person's professional activities during the past year. If he/she is in school as well as employed full time, instruct him/her to select his/her desired choice. If necessary, use CARD C of the P2_DEMO_REF reference card for him/her to review and provide the appropriate response.

If the guardian is on temporary medical leave, proceed to question 1230.

If the guardian is a student, has never worked, or he/she doesn't wish to answer, stop and do not complete the rest of the form.

The research coordinator will complete the information in the shaded box at the end of the form.

Questions 1210 and 1220. If participant/guardian is unsure of his/her last date of employment, explain to him/her to give a best estimate as to when he/she was last employed. The responses to Q1210 and Q1220 should make a partial date in the format of MM/YYYY. If the requested month and/or year is unknown of last employed, coordinators will use 98 for month and 9898 for year.

Questions 1240 and 1250. Must be completed by the Research Coordinator regarding where the CRF was completed and who completed the CRF.

Questions 1260 – 1280. Q1260 asks if the Research Coordinator reviewed the CRF during the in-person visit, if the form was participant completed. If Q1260 is answered 'Yes', the Research Coordinator must sign and date the form in Q1270 and Q1280.

For more specific details pertaining to completion of the form, see Demographics in Section 1.

2.4 ADMINISTRATIVE FORMS AND INSTRUCTIONS

This section provides specific instructions needed to complete the ASSESS-AKI administrative forms. These forms are not entered into the study database and are not submitted to the DCC. The instructions for each form are in alphabetical order based on form code (found in the lower right-hand corner of each form).

The following information is provided for each form: the purpose of the form, who completes the form, when the form should be completed, and form instructions. If you are unable to find the specific information needed to complete a form, please contact the DCC Primary Data Manager.

2.4.1 Case Participant Assignment Log (CASE_PART_ASSIGN)

Purpose: This form keeps a log of all enrolled participants who have experienced an AKI episode and are referred to as case participants.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visit 0

Form Instructions:

The case participant assignment log must be used every time a new case participant ID number is assigned. The CASE_PART_ASSIGN log is pre-numbered and a case participant will be assigned the next sequential number on the log.

At Visit 0, complete the three initials for the participant. The letter 'X' should be used if the case participant does not have a middle initial. In the event that two case participants have the same initials a fourth letter may be used to differentiate between the two case participants. The case participant initials must be the same initials documented in the ASSESS-AKI registry. The case participant's name should be written last name, first name on the case participant assignment log.

During the time between the index hospitalization (Visit 0) and the successful completion of the 3-month visit (Visit 3M), the case participant will be temporarily matched to one, two, or three control participants. The last 4 digits of each control participant's ID should be listed next to the case participant's name on the log.

Within 6 months after the case participant successfully completed Visit 3M, a control participant will be officially matched to each case participant. The Research Coordinator will perform the match using a matching module within the data entry application. Once the match is verified and entered into the database, the control participant's last 4 digits should be circled on the CASE_PART_ASSIGN log to identify the final control for the case.

If a control participant withdraws from the study before his/her 3-month visit, another control participant may be matched with the case participant.

This log will be stored at the clinical center and should not be sent to the DCC.

This log will be reviewed during ASSESS-AKI site visits.

2.4.2 Control Participant Assignment Log (CTRL_PART_ASSIGN)

Purpose: This form keeps a log of all control participants (those who have not experienced an AKI episode) enrolled into the ASSESS-AKI study.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visit 0

Form Instructions:

The control participant assignment log must be used every time a new control participant ID number is assigned. The CTRL_PART_ASSIGN log is pre-numbered and a control participant will be assigned the next sequential number on the log.

At Visit 0, complete the three initials for the control participant. The letter 'X' should be used if the control participant does not have a middle initial. In the event that two control participants have the same initials a fourth letter may be used to differentiate between the two control participants. The control participant initials must be the same initials documented in the ASSESS-AKI registry. The control participant's name should be written last name, first name on the control participant assignment log.

This log will be stored at the clinical center and should not be sent to the DCC.

This log will be reviewed during ASSESS-AKI site visits.

2.4.3 Data Processing Cover Sheet (DPCS)

Purpose: This form assists the clinical center and the DCC with the tracking of all data collection packets/forms from the time of collection at the clinical research center to the final processing at the DCC.

Who: An ASSESS-AKI Research Coordinator and DCC personnel complete the form.

When: This form is completed each time a data processing activity is performed.

Form Instructions:

Complete the Participant ID number, Participant initials, Visit number, and Form type being processed. A visit date is only required for form type 'Single (S)'. Response to a query is only completed when a form is being sent to the DCC per a query from the DCC. This is an indicator used by the DCC to flag queried items so they may be resolved in the Error Tracking module quickly.

The person completing the data processing activities (reviewing completed forms, registrations and first data entry, and collating of the forms) should record the current date and his or her coordinator ID number for each activity. Multiple ID's can be listed for an activity so if more than one person is involved in completing the activity, these can all be listed. This is used by the DCC for Quality Control purposes in identifying any problems with the packets or issues noted in processing of the forms.

Clip the Data Processing Cover Sheet (DPCS) to each visit packet and each single form before completing any data processing activity.

For more details on the Data Processing Cover Sheets (DPCS), refer to Section 11 of the ASSESS AKI General MOP.

2.4.4 Event Information Sheet (EVENT_INFO)

Purpose: This form records information on each individual hospitalization/ER visit, procedure or test the participant encounters throughout the life of the study.

Who: An ASSESS AKI Research Coordinator completes the form.

When: The Medical Event Questionnaire (P1/P2_EVENTS) form prompts the investigation of medical records which facilitates the completion of this form. The Research Coordinator must have a medical release signed by the participant to secure the medical records to complete this form.

Form Instructions:

Record the question number and annotation number from the Medical Event Questionnaire (P1_EVENTS/P2_EVENTS) form that corresponds to the event described on this form.

Document a brief description of the event and the type of visit either inpatient or outpatient.

The admission/start date and the discharge/stop date will document the length of the event.

Record the institution's name, address, and physician involved in the event.

It should be maintained and filed in the participant folder at the site.

This admin form contains confidential participant information and must not be sent to the DCC.

2.4.5 Adult Contact Information (P1_CONTACT)

Purpose: This form records detailed information about the adult participant to document emergency contacts and aid the Research Coordinator's contact with the adult participant throughout the study.

Who: An ASSESS-AKI Research Coordinator or participant completes the form.

When: Visit 0 and will be updated at each study contact.

Form Instructions:

The Adult Contact Information (P1_CONTACT) form must be completed at Visit 0.

As contact information changes, updates may be made directly on the Adult Contact (P1_CONTACT) form, or if necessary, complete a new form.

It should be maintained and filed in the participant folder at the site.

This administrative form contains confidential participant information and must not be sent to the DCC.

This form will be reviewed during site visits.

2.4.6 Pediatric Contact Information (P2_CONTACT)

Purpose: This form records detailed information about the pediatric participant and his/her guardian(s) to document emergency contacts and aid the Research Coordinator's contact with the pediatric participant throughout the study.

Who: The participant, participant's parent/guardian(s), or Research Coordinator completes the form.

When: Visit 0 and is updated at every study contact.

Form Instructions:

The Pediatric Contact Information (P2_CONTACT) form must be completed at Visit 0.

As contact information changes, updates may be made directly on the Pediatric Contact (P2_CONTACT) form, or if necessary, complete a new form.

It should be maintained and filed in the participant folder at the site.

This administrative form contains confidential participant information and must not be sent to the DCC.

This form will be reviewed during site visits.

2.4.7 Social Security Collection (SSN)

Purpose: To record the US participant's social security number (SSN). This number will be used search for records on participants who are lost to follow up.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: Visits 0, 3M

Form Instructions:

Note: This form is not required for the Montreal and Ontario sites. The form should be present for ALL other sites to document the participant's decision regarding use of their SSN number.

Question 1. If the participant did not sign Informed Consent for use of the Social Security Number for research purposes, STOP here and store the form in the participant's study folder as documentation.

Question 2. If the participant consented to the use of the SSN and is enrolled at a US site, record the SSN.

This administrative form contains confidential participant information and must not be sent to the DCC.

2.4.8 Visit Procedure Checklists

(INPATIENT_CHK, V0B_CHECK, OUTPATIENT_V3MCHK, OUTPATIENT_PC_CHK, OUTPT_VISIT_CHK1, OUTPT_VISIT_CHK2, and OUTPT_VISIT_CHK5)

Purpose: To provide the Research Coordinator with a checklist of all procedures and form that must be completed and those that are optional during a study contact.

Who: An ASSESS-AKI Research Coordinator completes the form.

When: At the specified study contact and when a participant misses a study contact.

Form Instructions:

This form serves as a guide to the Research Coordinator and should be sent to the DCC, in front of the visit packet or single form.

For all procedures and forms, indicate whether or not the procedure or form was completed. If it was not completed, indicate the reason in the comment field.

If the visit is missed, complete the checklist indicating the missed visit and send the completed checklist to the DCC.

This form is not entered during data entry.

ASsessment,
Serial Evaluation, and
Subsequent Sequelae in AKI
NIH/NIDDK

Quality of Life and Cognitive Function Manual of Procedures (QOL MOP)

Version:

January 1, 2015

1 MODIFIED MINI-MENTAL STATE EXAM (3MS)

Cognitive function assessment will be measured by the Modified Mini-Mental Status Examination (3MS). The 3MS will be conducted during the 3-, 12-, and 36-month, adult, in-person visits, although it can also be conducted by telephone in participants who are not able to complete an in-person study visit. We also note that cognitive function will not be performed in enrolled pediatric participants as the 3MS is not possible to administer reliably in these participants.

1.A General Instructions

Place the sentence writing and drawing in the participant study file.

Use the instructions on the form.

If you cannot determine whether an answer is correct, record notes next to the question and ask a supervisor to review the scoring later.

Make sure participant is attentive before each question.

(At bottom of each question sum the total for that question and enter it in the box provided on page 9.)

1.A.1 Q1a-Q1e Date/Place of Birth

Question 1 is a measure of long-term memory. It is assumed that everyone has had repeated opportunities to learn and report his/her date and place of birth.

1a-1c When were you born

Fill in the month, day, and year reported by the participant.

If partial or unrelated information is given, clarify the question by telling the participant you are looking for the month, day, and year in which he/she was born.

1d-1e Where were you born

If the participant gives only a partial answer (e.g., only the city/town), ask for the missing information.

If an unrelated answer is given (e.g., hospital name), clarify the question by telling the participant you are looking for the city/town and state or country in which he/she was born.

In rare instances, the participant may state that they have been born in rural areas, not a town. Ask the participant to name the postal address of the town through which he/she received mail. If he/she still says there is no town, the location that the participant considers to be his/her place of birth and routinely uses on documents when this question is asked (e.g., county, parish) is acceptable.

When the participant gives a response, record the city/town and state/country reported. Mark items as follows:

1. Correct: Mark if the participant gives a correct response.
2. Incorrect: Mark if the participant gives an incorrect response, no response,refuses to answer, or says that he/she can't remember.

SCORING NOTE:

Add up the total correct for 1a-1e and enter it in the box labeled, "Question 1 Total Score".

1.A.2 Q2a – Q2C Registration

- Use the instructions on the form.
- Use the words printed on the form you are administering.
- Make sure the participant is attentive when beginning the question.
- Say the three words distinctly at the rate of approximately 1.5 seconds per word.
- The participant may repeat the words in any order.
- If the participant repeats each word right after you read it, at the end of your presentation say, "Tell me the three words again" and mark the score according to the responses to this request.
- Do not repeat the words for the participant until after the first trial. If there are errors on the first trial, repeat the items up to five times until they are all learned (for a maximum of 6 presentations).
- Be sure that the correct suffix of the word is repeated. For example, do NOT accept "sock" for "socks" or "charitable" for "charity". The exact form of the word must be repeated.
- Record the number of presentations necessary for the participant to repeat all three words correctly (up to 6).
- Add up the total correct for 2a-2c and enter the number in the box labeled, "Question 2 Total Score".

1.A.3 Q3a-Q4b Mental Reversal

This item has two parts: counting backward from 5 to 1 and spelling WORLD backward. For each part, ask the participant to do the forward version first. Coach once when needed.

1.A.4 Q3a-Q3b Count from 1 to 5

Instruction: "I would like you to count from 1 to 5." Wait as the participant counts.

- If the participant cannot count forward to 5, prompt with "Say, 'one, two, three, four, five'" at the rate of 1.5 seconds per digit.

- Coach only once, and then continue with Question 3b, even when the performance in counting forward is not perfect.

Instruction: “Now I would like you to count backward from 5 to 1.”

- Record the first 5 numbers in the order given in the blanks provided.

If no response is given, please enter a dash (“-“) in the box.

- Record the number of errors in the boxes provided.
- Question 3 Total Score = 3b score.

1.A.5 Q4a-Q4b Spell “WORLD”

Instruction: “Spell ‘WORLD’.” Wait as the participant spells.

- If the participant cannot spell ‘WORLD’ forward, prompt with, “It is spelled W-O-R-L-D,” at the rate of 1.5 seconds per letter.
- Coach only once, and then continue with Question 4b, even when the performance in spelling forward is not perfect.

Instruction: “Now spell ‘WORLD’ backwards.”

- Record the first 5 letters in the order given by the participant in the blanks provided.
- If no letter is given, please enter a dash (“-“) in the box.
- Enter the number of correct responses in the boxes provided.

1.A.6 Q5a-Q5c First Recall of Three Words

Instruction: “What three words did I ask you to remember earlier?”

- The words may be repeated in any order.
- For each word readily reported, check:
  - 3 Spontaneous recall

NOTE: Do not wait more than 3 seconds for spontaneous recall.

If the participant repeats an incorrect form of the word or repeats the word only after cueing, check the appropriate rating as follows:

- 2("first 2") – Correct word/incorrect form. If the participant repeats an incorrect form of the correct word (e.g., "sock" for "socks" or "charitable" for "charity"), mark the "first 2" to reflect this answer. In these cases it is very important to repeat the word with the correct ending back to the participant for the subsequent recall.
- 2("second 2") – Correct recall after cueing. For each word not readily reported, provide the cue under this second "2" (i.e., "It is something to wear").

NOTE: Do not wait more than 2 seconds after giving the cue before providing the next level of help.

- If the participant cannot give the correct answer even after multiple choices, check:
  - 0 Unable to recall/refused.

An inaccurate response was given after both prompts or the appropriate time limit has elapsed.

NOTE: Tell him/her the correct answer for the benefit of the second recall to be requested later.

EXAMPLE:

Examiner: "What three words did I ask you to remember earlier?"

Participant: "Socks… (3 seconds elapsed)"

[Examiner would check, "3 – Spontaneous recall" for "socks", and then would go on to give the category prompt for the remaining two words.]

Examiner: "Another word is about a color."

Participant" "Blue!"

[Examiner would check the "second 2" for "blue" and give the next category prompt for the remaining word.]

Examiner: "Good. Another word is about a good personal quality."

Participant: "Modesty?"

[Examiner now provides the choice of three alternatives for charity listed under "1".]

Examiner: "I'll give you three words to choose from – honesty, charity, modesty."

Participant: "Modesty!" (Or, for example, no response after 2 seconds:

[Examiner would now check "0" for charity and tell the participant the target word (i.e., "charity").]

Examiner: "No, The word is 'charity'."

[Examiner now enters the total score for Questions #5. The total score is the sum of 5a, 5b, 5c. For each item, only one box can be checked and the sum total cannot be greater than 9]

1.A.7 Q6a-Q6c Temporal Orientation

Write all answers verbatim. If the participant gives no answer or the question is not even attempted, mark an "X" on the adjacent line.

6a Today's date

Instruction: Ask the participant: "What is today's date?"

- Record the participant's answer verbatim.
- If no response is given enter "X".
- Mark the box that corresponds to the level of accuracy given in the participant's response.

6b Season of the Year

Instruction: Ask the participant: "What season of the year is it?"

Since distinctions between seasons can be difficult during certain months, the following schedule has been created. For months with two seasons listed, either answer is correct.

Month	Correct Response
January	Winter
February	Winter
March	Winter or Spring
April	Spring
May	Spring
June	Spring or Summer
July	Summer
August	Summer
September	Summer or Fall
October	(Autumn)
November	Fall (Autumn)
December	Fall (Autumn) Fall (Autumn) or Winter

1.A.8 Q7a-Q7d Spatial Orientation

For these questions, mark:

2 Correct: (for 7a only) Mark if participant answers correctly.

1 Correct: Mark if participant answers correctly.

0 Incorrect: Mark if participant answers incorrectly for any reason.

Write all answers verbatim. If the participant gives no answer, mark an "X" on the adjacent line.

- Enter the Total Score for question 7.

7a State

Ask: "What state are we in?"

2 Correct

0 Incorrect

7b Country

Ask: "What country are we in?"

1 Correct

0 Incorrect

7c City/Town

Ask: "What (city/town) are we in?"

1 Correct

0 Incorrect

7d Clinic, store, home

Ask: "Are we in a clinic, store, or home?"

1 Correct

0 Incorrect

This question assumes that the test is being administered in a clinic setting. When the correct answer is not among the three alternative (e.g., test is being conducted in a hospital or nursing home), substitute the correct response for the middle alternative (store).

If the participant responds that neither “clinic”, “store”, nor “home” is the correct answer, ask him/her to make the best choice out of the three options.

1.A.9 Q8a-Q8e Naming

This set of questions test whether or not the participant can promptly name the five body parts.

Mark items:

1 Correct: Mark if participant answers correctly.

0 Incorrect: Mark if participant answers incorrectly for any reason.

Ask: “What do you call this part….?”

Ask each question while pointing to the appropriate part of your body.

Correct responses for each item are:

- 8a – forehead or brow
- 8b – chin
- 8c – shoulder or shoulders
- 8d – elbow or elbows
- 8e – knuckle or knuckles

If the participant gives a scientific or medical version of the name for any of the body parts (e.g. “olecranon”), ask him/her to provide the common name.

If the participant cannot name the item within 2 seconds or gives an incorrect answer, do not help or question again. Mark “0” and continue with Question 9.

- Enter the Total Score for question 8.

1.A.10 Q9 Four-legged Animals

Ask: “What animals have four legs? Tell me as many as you can.”

- Record each animal named in the spaces provided.
- If the participant says, “All animals have four legs,” say “Tell me their names.”
- Discontinue after 30 seconds. Record the total number of correct responses.
- If the participant gives no response for 10 seconds and there is still at least 10 seconds remaining, gently remind him/her (once only):

Ask: “What (other) animals have four legs?” If he/she still gives no response, record “00”.

The first time an incorrect answer is provided, say “I want four-legged animals.” Do not correct for subsequent errors.

- Score one point for each correct animal.
- Accept marginal cases such as:
  - Monkey
  - Chimp
  - Baboon
  - Kangaroo
- Different names for the same animal of different ages or sex count as one animal. For example:
  - Kitten/cat
  - Puppy/dog
  - Deer/doe
- Those animals with similarities, but true technical differences, may be counted as two separate animals; e.g. pony and horse may be counted as two; mule and donkey may be counted as two; but ass and donkey are the same animal and must be counted as one.
- Other oddities:
  - A sea lion does not have four legs
  - A seal does not have four legs
  - A platypus is acceptable

Example Instructions:

Examiner: “What animals have four legs? Tell me as many as you can.”

Participant: “Dog…Cat…Bird…”

Examiner: “I want four-legged animals.”

Participant: “Oh, ok! Elephant...”

(Ten seconds pass and there are still ten seconds left of the 30 seconds.)

Examiner: “What other animals have four legs?”

Participant: “Hippo…Dog…Kitten…Cow…Pig…Chicken…Sheep…”

(Thirty seconds are up.)

- Enter the Total Score for question 9.

1.A.11 Q10a-Q10c Similarities

This question is designed to measure abstraction or conceptual thinking. In general, points are given for conceptual similarities that are primarily pertinent for both members of the pair. No prompting or coaching is allowed except for 10a. Always accept the first answer given. If two concepts are given simultaneously (e.g. within the first statements provided back by the participant), score the higher value of the two concepts.

10a Arm and a leg

Ask: "In what way are an arm and a leg alike?"

- Mark "2" when the response is that they are both:
  - Limbs
  - Extremities
  - Appendages
- Mark "1" when the response is that both:
  - Are body parts
  - Bend
  - Move
  - Are long
  - Other similar responses
- Mark "Error" when the participant gives an incorrect similarity, tells how they are different, says "They are different," or "I don't know", or refuse to answer. Other examples of "0" answers:
  - Fingers and toes

If the initial response is scored "1" or "0", coach the participant by saying "An arm and a leg are both limbs or extremities" to reinforce the correct answer. Coach only for Question 10a. NO other prompting or coaching is allowed for 10b or 10c.

10b Laughing and crying

Ask: "In what way are laughing and crying alike?"

- Mark "2" when the participant responds that they are both expressions of:
  - Feelings
  - Emotions
- Mark "1" when the participant responds that both are:

  - Sounds
  - Expressions
  - Both have tears
  - Both are satisfying to you
  - You cry with both
  - Other similar responses
- Mark "Error" when the participant gives an incorrect similarity, tells how they are different, says "They are different" or "I don't know", or refuses to answer. Other examples of "0" answers:
  - When you laugh, you laugh; when you cry, you cry.

10c Eating and sleeping

Ask: "In what way are eating and sleeping alike?"

- Mark "2" when the response is that they are both:
- Mark "1" when the response is that both are:
- Mark "Error" when the participant gives an incorrect similarity, tells how they are different, says "They are different," or "I don't know", or refuses to answer.
- Enter the Total Score for question 10.

1.A.12 Q11-Q12 Repetition

11 Would like to go out

"Repeat what I say: 'I would like to go out.'"

- Pronounce the individual words clearly but with normal tempo of a spoken sentence.
- Mark "Correct" when the sentence is repeated exactly.
- Mark "1 or 2 words missed" when one or two incorrect words are given.
- Mark "3 or more words missed" when three or more incorrect words are given, there is no response or the participant refuses.
- Enter the Total Score for question 11.

11-12c No ifs, ands or buts

"Now repeat: 'No ifs, ands or buts.'"

- Mark "Correct" for each part (e.g. no ifs, ands, or buts) correctly repeated; given no credit if the participant misses the "s".

- Mark “Incorrect” when the word is not correctly repeated (including when the “s” is not pronounced), no response is given or the participant refuses.
- Enter the Total Score for question 12.

1.A.13 Q13 Close your Eyes

Hold up the “Close Your Eyes” card and say “Please do this.” (Appendix A)

- If the participant does not close his/her eyes within 5 seconds, prompt by pointing to the sentence and saying. “Read and do what this says.”
- If the participant has already read the sentence aloud spontaneously, simply say, “Do what this says.” Allow 5 seconds for the response.
- As soon as the participant closes his/her eyes say: “Open.”
- Mark 3 – “Closes eyes without prompting” when participant performs the command only after the prompt: “Read and do what this says.”
- Mark 1 – “Read aloud, but does not close eyes “when participant reads the command aloud either spontaneously or after the prompt, but does not close his/her eyes.
- Mark “0” – “Does not read aloud or close eyes” when the participant neither reads the sentence aloud nor closed his/her eyes, or otherwise does not respond.
- Enter Total Score for question 13.

1.A.14 Q14a-Q14e Writing

“Please write the following sentence: ‘I would like to go out.’”

- Hand participant a piece of blank paper and a standard lead pencil with eraser. If necessary, repeat the sentence word by word as the participant writes.
- Allow a maximum of 1 minute after the first reading of the sentence for scoring the task.

NOTE: If the participant is still working at the end of one minute, allow him/her to complete the task for the sake of maintaining rapport and morale. Mark the 1-minute point on the list of words and do not give credit for parts finished after 1-minute.

- Mark “Correct” for each completely correct word, except “I”.
- The following are considered acceptable:
  - Printing or cursive writing
  - All capital letters or all lower case letters
  - Self-corrected errors
- The following are considered errors:
  - Portions of sentence written after the one minute time limit

  - Spelling errors
  - Incorrect mixed capitalizations, e.g. I Would Like To Go Out.
- Mark “Incorrect” for each word which has any error listed above or if the participant does not respond.
- Enter the Total Score for question 14.

1.A.15 Q14f Hand Used for Writing

Observe which hand the participant uses to write the sentence on question 14. You will need this information later in question 16. If this task was not performed, ask the participant if they are right- or left-handed and record.

1.A.16 Q15a-Q15c Copying Two Pentagons

Say: “Here is a drawing. Please copy the drawing onto this piece of paper.”(Appendix B)

- Present the participant with the Construction Stimulus page. Allow one minute for copying.
- For right-handed participants, present the sample on the left side; for left-handed participants, present the sample on the right side.
- Allow a maximum of 1 minute for response.

NOTE: If the participant is still working at the end of one minute, allow him/her to complete the task for the sake of rapport and morale. Mark the 1-minute point on the drawing and do not credit for parts finished after 1 minute.

1.A.17 Q15a-Q15b Pentagons

Scoring:

- Do not penalize for self-corrected errors, tremors, minor gaps or overshoots
- When gaps are found in the drawing, they are permissible if the shape of the pentagon can be perceived.

Each pentagon is scored as follows:

- Mark “4” when there are 5 approximately equal sides
- Mark “3” when there are unequal sides, and the longest: shortest side ratio is >2:1.
- Mark “2” when another enclosed figure is drawn.
- Mark “1” when there are 2 or more lines, but it is not an enclosed figure.
- Mark “0” when there are less than 2 lines or the participant refuses to do the task.

1.A.18 Q15c Intersection

The intersection is scored as follows:

- Mark “2” when there is a 4-cornered intersection
- Mark “1” when it is not a 4-cornered intersection
- Mark “0” when there is no enclosure or the participant refuses to do the task.
- Enter the Total Score for question 15.

1.A.19 Q16a-Q16c Three-stage Command

Hold up the piece of paper in plain view of the participant, but out of his/her reach and say:

“Take this paper with your left hand (right for a left-handed person), fold it in half, and hand it back to me.”

- Refer to Question 14f to check whether the participant is right- or left-handed. Ask him/her to take the paper in his/her non-dominant hand.
- After saying the whole command, hold the paper within reach of the participant.

NOTE:

- Do not repeat any part of the command.
- If the participant requests the examiner to repeat a portion of the command and it is felt appropriate to oblige for sake of maintaining rapport, score according to the participant’s response(s) before repeating the command.
- Do not move the paper toward the participant.
- Do not move your hand toward the participant as a gesture to take the paper back.
- If the participant reaches for the paper right after hearing the first portion of the command, move your hand away from the participant so that the paper is out of each and continue to state the next two parts of the command without interruption.
- The participant may hand back the paper with either hand.
- Mark “Incorrect” for each portion of the command incorrectly completed, including:
  - First portion: participant uses dominant/preferred hand
  - Second portion: participant folds the paper more than once
  - Third portion: participant puts the paper down instead of handing it back to the examiner
  - Participant refuses to do the part of the task
- Enter the Total Score for question 16.

1.A.20 Q17a-Q17c Second Recall of Three Words

"What three words did I ask you to remember earlier?"

- Administer this item even when the participant scored one or more "zeros" on Question 5.
- The words may be repeated in any order. Do not wait more than 3 seconds for spontaneous recall.
- If participant cannot give the correct answer after a category cue, provide the three choices listed.
- Do not wait more than two seconds after category curing for a response.
- If the participant still cannot give the correct answer from the three choices, mark "0" and provide the right answer.
- If the participant repeats an incorrect form of the correct word, e.g. "sock for "socks" or "charitable" for "charity", a score has been added to reflect this answer ("Correct word/incorrect form" Score = 2).
- If the participant gives an incorrect answer in the correct category (e.g. says "shoes" or "coat: when the correct answer is "socks"), provide the three alternatives for him/her to choose from, and score "1" if the choice is correct.
- If the participant cannot get the correct answer even after multiple choices or an incorrect response is given after both prompts or when the appropriate time limit has elapsed, mark "Unable to recall/refused".
- Mark "Unable to recall/refused" if an incorrect response is given after both prompts, or when the appropriate time limit has elapsed.
- Provide the correct answers.

Example Instructions

Examiner: "What three words did I ask you to remember earlier?"

Participant: "Socks…" (3 second pause)

Examiner: "Another word is about a color."

Participant: "Blue!"

Examiner: "Good. Another word is about a good personal quality."

Participant: "Modesty?"

Examiner: "I'll give you three words to chose from – honesty, charity, modesty."

Participant: Modesty!" (or, no response for 2 seconds)

Examiner: "No, the word is 'charity'"

For the above example the scores are 3, 2, and 0 respectively, for socks, blue and charity.

- Enter the Total Score for question 17.

1.A.21 Q18 Special Problems

If physical/functional disabilities or other problems exist that cause the participant difficulty in completing any of the tasks, mark the box coded “Yes” and record the nature of the problem from the following problems codes:

- Vision
- Hearing
- Writing problems due to injury or illness
- Language
- Literacy/lack of education
- Other (please record the specific problem in the space provided)

If no special problems were noted, mark “No”.

1.B Modified MMSE Scoring Tally Sheet

- The total score for each page should be recorded here.
- Sum the page totals and enter Modified MMSE Total Score.

2 MODIFIED MINI-MENTAL STATE EXAM – TELEPHONE VERSION

The cognitive assessment for this interview is the Modified Mini-Mental State Examination – Telephone Version (T-3MS). Modifications were made to the 3MS for phone administration but an attempt was made to retain most items from the original 3MS.

Prior to conducting cognitive assessments with a participant, it is important to consider some basic issues of testing.

2.A Establishing Rapport

In this context, rapport refers to the interviewer's efforts to engage the participant's interest in the test, elicit their cooperation, and encourage them to respond in a manner appropriate to the objectives of the test.

The interaction between the interviewer and participant will affect the participant's performance. In a telephone interview, it will be more challenging to establish rapport because you do not have the benefit of interpersonal interactions such as eye contact, smiling, nodding and other supportive gestures. Do your best to maintain an upbeat and natural tone of voice without compromising standardization of the testing.

Standardized administration is critical, but the participant should also be comfortable and have a pleasant experience. Neuropsychological testing can be quite threatening to some people. Establishing rapport with the participant is essential so that they are at ease and are able to give their best performance during testing. A participant who is anxious or uncomfortable will be too distracted to perform at their best. In particular, older participants may be more likely to feel anxious in a test setting and may be sensitive about being evaluated.

2.A.1 Tips on Establishing Rapport

1. Try to establish rapport and put the participant at ease before you begin. Engage in a bit of casual conversation before testing.
2. Always be pleasant and patient.
3. Be sure to give the participant a good idea of exactly what will happen during the interview session before you begin. Say something like, "First we'll complete some short tests of memory and thinking and then we'll complete some other questions. The whole session should take about 45 minutes." Knowing what to expect may help to allay the participant's fears.
4. Introduce cognitive testing by saying something like, "Now I'm going to ask you some questions to test your thinking and memory abilities. Some may seem easy for you while others will seem difficult. Very few people obtain perfect scores. Just try your very best on every question. OK?"
5. Give encouragement, especially if the participant seems worried or distressed. Use phrases like "You're doing fine" and "Just try your best".
6. Do not rush any of the aspects of your interaction with the participant. Adults are likely to be uncomfortable with someone who walks or talks to fast, or rushes them with the testing. Allow participants sufficient time to respond and to ask questions.

7. Check to make sure the participant is comfortable before testing (e.g. warm enough, need to use the restroom, etc.).
8. If a participant becomes frustrated with the relevance of a particular task, it can often help to explain the general purpose of the task. For example, say, "This is a test of concentration or thinking." Try not to provide too much specific information as this may raise anxiety.
9. Keep in mind that each participant's personality will be different and some will respond better to you than others. Adjust your interaction with them accordingly. For example, keep a slower pace for those who require it, and move more quickly for those who prefer that kind of interaction. Always thank the participant at the end of the session. Say something like, "I want to thank you for your participation today and I need to remind you not to discuss the specifics of the tests with anyone. I really appreciate your effort, attention, time (whatever is appropriate). It was a pleasure working with you."
10. Keep in mind that we cannot conduct our research without participants dedicating their time and effort – make sure the participant knows how much he or she is appreciated.

2.B Standardized Administration

It is critical to follow standard administration protocol; however, you need to achieve a balance between maintaining your rapport with the respondent and using the standardized procedures. Often times, interviewers think that following standardized protocol means they must read the questions in a monotone voice and inhibit their remarks to only the bare minimum. From the participant's point of view, this transforms the interviewer from a warm, respectful person to a robot. This will undoubtedly affect rapport and probably affect the participant's performance.

It is possible to follow the standardized protocol while still maintaining rapport with the participant by being familiar and comfortable with the test instructions and by responding flexibly. If you've established strong rapport, most participants will be very cooperative and will follow whatever directions you provide.

2.B.1 Setting for Administering Cognitive Screening Tests

1. The room where the participant is located should be private and quiet. This will be confirmed at the beginning of the telephone interview. In addition, the interviewer should be in a private, quiet room without distractions.
2. Observers are not allowed to be present during testing.
3. The room should be free of distractions with proper lighting and temperature regulation and comfortable seating.
4. If possible, the participant may want to prevent interruptions by placing a "Please Do Not Disturb" sign on the door. This may be necessary if they are in a nursing home or other facility besides a private home.
5. Be prepared with all the materials you will need and put them within easy reach. This will minimize fumbling, paper shuffling, and searching throughout the session.

2.B.2 General Testing Rules

1. Administer all test according to the standardized directions outlined in the interview booklet
2. On tests where a spoken answer is required, record the participant's response verbatim (word-for-word).
3. On tests that are timed, you must use a stopwatch. Do not rely on the second hand of your wristwatch.
4. Do not refer to tests by their names or by the domain they evaluate. For example, don't say "Now we're going to do the Recall of Three Words" or "The next test measures your recall." If you feel it's necessary, at the end of the section, you may transition to the next items by saying something like, "Good. Now, let's go on to something else." Or just continue with the next item.
5. Under ordinary circumstances, you should not tell the participant whether a specific response is correct or incorrect. If they ask, say something like, "You're doing fine. Let's try this one." If the participant insists on knowing, simply reply, "I'm really not allowed to say."
6. It is acceptable to give some general information about tests if the participant asks, as long as doing so will not compromise future testing. For example, you would not want to answer the participant who asks after the T-3MS "So, who is the President of the United States now?" It is acceptable to answer a question like, "So what is that test supposed to measure?" after it has been administered.
7. Make a note on the interview booklet of any unusual events during testing such as distraction by a ringing telephone or fire alarm, or interruption by a third party. Also make a note of anything the participant says that might affect how the results are evaluated such as, "I've taken this test before," or "I feel dizzy."
8. Be prepared to make accommodations for hearing or speech problems. In case of hearing impairments, be sure to speak in lower tones and do not speak too quickly. If the participant's speech is unclear or slurred it may be difficult to understand their responses to questions where you need to ask them to repeat something.
9. Be flexible, but try to adhere to standardized test administration without being rude. For example, if a participant begins to tell an involved story, say something like, "I don't want to interrupt, but we really need to move along with the interview. Would you mind finishing your story when we're all through?"
10. Allow participants to refuse tests only when they are clearly to upset or frustrated to continue. Try to avoid refusals by offering a break or switching to another task.
11. Avoid giving a break to the participant during the T-3MS unless required. If the participant asks for a break and it seems as if they could wait until the end of the testing, ask if they're willing to do so. If the participant requires a break at an inconvenient time in the middle of a test, ask if it would be possible to continue for another __minutes. Obviously, if there is an emergency (restroom break needed, fire alarm, extreme fatigue or frustration), take a break, but note exactly the point at which the break was taken and the duration of the break.
12. Purposeful self-correction is allowed on all tests. Follow test specifications for scoring.

2.B.3 Recording Rules

1. Record items on the interview booklet in pencil or pen. No erasing is permitted in the interview booklet. If an error is made cross it out once and write the correct answer next to it.
2. Do field edits in pen or pencil.
3. Never leave blanks. If the participant skips a question, record this on the interview booklet. If the participant gets an item correct, fill in a checkmark where appropriate.
4. Record clock times where indicated.
5. Record any unusual circumstances.
6. Record /X/ on the interview booklet if the examiner asks the participant for clarification on an item. Also record the question that the examiner asked and the response given by the participant.

2.C Additional Considerations

1. If the participant has a problem hearing, seems to have been distracted during instructions, or seems to have misunderstood you, repeat the instructions as needed.
2. It is generally acceptable to give neutral, clarifying probes (e.g. repeat the question, ask "Can you tell me another name for _____," etc.) However, do not provide much information. Too much information would be, for example, telling the participant, "The past vice-president's name starts with a 'G'."
3. Probes should be given for ambiguous answers or situations. If a response is clearly wrong, do not probe unless you question whether or not the participant heard or understood you.
4. All neutral probes should be recorded with an /X/ for query. If you inadvertently gave too much information in a probe, you can mark this with an /X/: gave hint, "VP's name starts with a 'C'", or some similar notation.
5. For items with standard prompts, follow the instructions.
6. As with the other portions of the interview, always probe a "Don't Know" response at least once. If the response remains, "Don't Know", then score is zero.
7. Do not leave any RECORD spaces blank. To editors, a blank space means you did not administer the items. If the participant has refused to answer the question, write RF in the space.
8. During administration, you may want to use abbreviations for the sake of flow and to save time, but remember to fill in the information during your field edit. Acceptable abbreviations are provided for each question; if an abbreviation is NOT specified, do not use it.
9. Please write notes regarding any sensory limitations, unusual responses, or other behaviors in the space provided at the end of the T-3MS. Please be clear and concise in your comments.
10. Also include any notes about factors that may have influenced the participant's performance on the test. These may include the presence of a spouse, another phone ringing or other noisy distractions, participant's anxiety, etc. Please take special note of these and similar distractions, as they will be important in determining the proper Completion and Protocol Codes to be assigned after the test.

2.D Confidentiality

Any information about participants must be kept confidential. This includes testing results, interview responses, personal information obtained through conversation with participants or their family members, and even the fact that they are involved in the study. Do not discuss confidential information with any non-study personnel, including family members of the participant.

2.E Test Security

1. When practicing the T-3MS, try to use the Cache Study personnel as practice participants. There will also be structured practice sessions with designated senior volunteers. In answering questions, practice participants should "role play" and not give sincere responses. This serves to avoid evaluation of your colleagues and also provides different responses for practice.
2. Do not photocopy or distribute these tests to anyone unless instructed to do so by the field supervisor. Tests become invalidated if the general public becomes overly familiar with their content and specific purposes.

2.F Administration of the T-3MS

The T-3MS provides a general indication of the participant's cognitive abilities. It is a brief screening test (approximately 10 minutes) and assesses domains such as attention, orientation to time and place, new learning and memory abilities, expressive and receptive language abilities, abstract reasoning and other skills.
If the participant meets the scoring requirements on the T-3MS for informed consent, the rest of the interview will be administered. If the participant does not meet the scoring requirements, discontinue the interview. Unlike previous studies, we will not use a proxy informant to collect additional information about the participant. You should not skip the T-3MS or administer it later in the interview because it is part of the informed consent procedure.

It is important to keep in mind that the T-3MS is a research test (not a clinical test) and a screening instrument. As such, scores on the test will not provide any diagnostic information when administered in this context. You may need to explain this to the participant and address other concerns or anxieties about this test.

2.F.1 General Instructions

1. Read the introductory statement at the top of the T-3MS and record the time that testing started.
2. Read questions exactly as printed on the T-3MS.
3. Adhere to standardized instructions.
4. Record all responses verbatim in the spaces provided. Where indicated, abbreviations or check marks may be used.

2.F.2 Q1-Q5 Long Term Semantic Memory (Political Figures)

1. Give full credit if participant responds with on the last name.

2. If only the first name is given, probe to try to get the last name. (e.g. neutral probes, such as "Think about it and tell me what you can", or "Let me give you a moment to think of it', etc.).
3. Record the answers the participant gives whether it is correct or incorrect. If the participant says the correct answer after you have clearly moved on (e.g. you have completed reading the next question) score this as incorrect, and record where this occurred.

Abbreviations: Only the first initial is an accepted abbreviation on these items. Last names need to be recorded in their entirety.

2.F.3 Q6 Registration (Memory)

1. This item has been changed from using show cards to the interviewer reading the three words to the participant. There is an instruction asking the participant not to write anything down during this item. Other instructions remain the same.
2. If the participant makes errors, continue up to three trials, but score only the first attempt.
3. If participant repeats a form of the word (e.g. honest instead of honesty, shirts for shirt) consider these errors. Record with a check mark all correct responses. Write down all errors verbatim. Record the number of trials in the box provided.
4. Tell the participant to remember the words because you will ask him/her to recall them again later. Pause a few seconds afterward to allow the participant to think about this. During other portions of the T-3MS, if the participant asks what the words were, do not provide the words again unless you are following the standardized prompts during delayed recall trials.

Abbreviations: A check mark in the specific space is acceptable to indicate a correct response; be careful, however, because the exact word is needed to be considered correct.

2.F.4 Q7 and Q8 Mental Reversal

1. Count from 1-5; assist once if needed. For example, if the participant has not response, repeat the instructions "count from 1-5". You may provide the first two numbers to get them started (e.g. "1…2… what next?")

Abbreviations: A check mark in each space is acceptable to indicate a correct response.

2. Count backwards. If there is no response, do not provide help but repeat the question. Record verbatim and score.
3. Do not skip the backwards task if the participant makes errors counting forward. Only skip the backward counting task if the participant does not understand the nature of the task.

Abbreviations: None

2.F.5 Q9 and Q10 World Backward

If participant spells "word", repeat and clarify. You may even provide a definition to clarify that the word was "World". For example, you clarify the word as meaning earth or globe. Be certain to record this prompt.

Abbreviations: A check mark in each space is acceptable to indicate a correct response.

1. If participant is unable to spell at all (this does not include an error in spelling) or makes no attempt, assist once. For example, if the participant makes no response, repeat the instructions "Please spell the word world." You may provide the first letter to get him/her stated (e.g., "what…what comes next?"
2. Spell "World" backwards. No writing is allowed by the participant—(s) he must do this mentally.
3. If the participant misspells world ad w-o-u-r-l-d, but then spells it backwards as with "d-l-r-o-w" or "d-l-r-u-o-w", give full credit. In the first example, the participant may have self-corrected the initial misspelling; in the second example, (s) he accurately placed the letters in reverse order.
4. Do not skip the backwards-spelling task if the participant makes errors in spelling. Only skip the backwards-spelling task if the participant does not understand the nature of the task.
5. Record verbatim.

Abbreviations: None.

6. The correct backward spelling of world is written below the response lines. Any difference in letter position between the participant's response and correct spelling is counted as incorrect.
7. There are 5 possible positions ("___ ___ ___ ___ ___"). Write the participant's response in successive spaces. The number of letters that directly correspond to "D-L-R-O-W" is the participant's score. Examples:

D W O R L	3
D R L O W	3
D L – something – something W	3
D L O W	2
D L R O W	

For correctly placed letters, write a check mark on the line above the box where the letters are written.

2.F.6 Q11 First Recall of the 3 Words (Q17 Second Recall of the 3 Words)

1. Spontaneous Recall – 3 points per word. Instructions are the same as the original 3MS except that prompt number two is provided orally by the interviewer rather than on show cards.
2. If the participant is unable to recall words, use category prompts provided in the booklet. Check for correct responses or record incorrect responses.
3. If the participant still is unable to recall the words, use the prompts provided in the booklet in order and score accordingly. You may tell the respondent that her/his response was incorrect prior to providing the prompt.

4. If the participant is unable to recall the word after providing both prompts, tell them the correct word.

**Abbreviations: A check mark in each space is acceptable to indicate a correct response. Record incorrect responses verbatim.*

2.F.7 Q12 Temporal Orientation Items

At the beginning of this section, there is an instruction for the participant not to look at a watch or calendar for the next several questions. Be sure to read this instruction.

**Abbreviations:*

Year: None
Season: None
Day of week:

Mon = Monday	*Fri = Friday*
Tues = Tuesday	*Sat = Saturday*
Wed = Wednesday	*Sun = Sunday*
Thur = Thursday	

Note: If the participant offers a number of the day of the week instead of the name, probe as this is unclear; some may refer to the first day of the week as Sunday while others may refer to the first day of the week as Monday.

Month:

Jan = January	*Jul = July*
Feb = February	*Aug = August*
Mar = March	*Sept = September*
Apr = April	*Oct = October*
May = May	*Nov = November*
Jun = June	*Dec = December*

Note: If the participant offers a number instead of a name (e.g. "the first month of the year"), accept the response.

Date: None
State: UT = Utah
Town: None
Church, home, office: None

2.F.7.a Q12b Season

1. Full credit is given if response is within 1 week either direction of the correct season (e.g. a response if "summer" on June 13 is correct or a response of "spring" on June 27 is also correct).

Approximate date of seasons:

March 20 – June 20 is Spring	September 23 – December 19 is Fall

June 21 – September 22 is Summer December 20 – March 21 is Winter

2.F.7.b Q12d Month

1. Either the name of the month (e.g. July) or the number (e.g. 7) is acceptable.

2.F.7.c Q12g County

1. If possible, try to find out the county where the participant's town is located prior to the interview.
2. If resources are unavailable for you to do that, record the participant's response and make a note for QA to check the Zip Code directory during edit.

2.F.7.d Q12h Town

1. If the participant gives the name of a small community (and you know that it is correct), give credit. Record the response and make a note that it is correct according to your knowledge.
2. If you are uncertain about this, try to check a map when you do your field edit. If you don't have a detailed enough map of the state they are in, leave a note in the margin and the QA staff will confirm.

2.F.8 Q13 Expressive Language (Naming Body Parts)

1. The original 3MS had the participant name body parts in the response to a visual prompt (pointing). In this version, the participant names a body part in response to a verbal description provided by the interviewer/
2. If the participant provides incorrect responses that are in the vicinity of the correct body part (e.g. hair for forehead, beard for chin, finger for knuckle) request another response or clarify if appropriate. Please record on the test form what additional prompts you used (e.g. /x/ "No, the part of the face that is beneath the hair." Or /x/ "No, the part of the face that the beard grows on.") Please note that neutral probes are allowed.
3. If the participant provides the correct response for one of these items after you have moved beyond the question, mark this and record the response, but do not give credit.

**Abbreviations*: *A check mark in the space to indicate a correct response is acceptable.*

2.F.9 Q14 Naming (Verbal Fluency)

1. You will be using a stopwatch to ensure accurate timing. If the 20-second time period is interrupted for any reason (e.g. you can hear someone walk into the room and interrupting participant), discontinue the test and note the time spent on the trial. Tell the participant that you will re-administer this task later and do so at the end of the T-3MS.
2. Record responses verbatim. If participant gives one or two responses and then sites quietly or says they are finished, encourage them to continue – to keep trying until the 20 seconds are up.

3. If participant drifts off task and begins naming objects outside of the category (e.g. farm, field, etc.), repeat instructions "four legged animals". *Keep the watch going.*
4. Only unique examples are given credit. Write down all items, even repeats. During scoring, circle repeats or items outside the category and do not count (e.g. if "cow" is given twice, circle the repeat, and give only 1 point for the response "cow"). Give credit for a species name and any accompanying breeds within the species (cows, cats, dogs, etc.); male, female, and infant names of species. For example:

Responses	Point
Dog	1
Terrier	1
Mutt	1
Brown dog	0 – repetition
Puppy	1
Bitch	1
Fido	0 – proper noun
Unicorn	1
Grizzly bear	1
Brown bear	1

5. If the participant is responding too fast for your to write the words, you may abbreviate while writing. If you used abbreviations, fill in the words during the field edit.
6. Score = 1 point per correct item; maximum = 10. The participant may give you an unlimited number of items. If the participant gives you 20 correct items still score only 10 points.

**Abbreviations: None. If you use abbreviations during the 20 seconds, be sure to write out the entire word during the field edit.*

2.F.10 Q15 Abstract Verbal Reasoning

The general scoring criteria are as follows:

1. A correct answer which includes a general classification relevant for both members of a pair. — 2 points
2. A partly correct answer which included a specific property or function that is similar to both members of the pair. — 1 point
3. Incorrect answers may include specific properties or generalizations which are incorrect or are not necessarily true, differences between the members of the pair, or clearly incorrect responses. — 0 points

**Abbreviations: None.*

2.F.10.a Q15. Arm & Leg

1. If the participant does not give a 2-point response on the first item, state the standard prompt. If the participant gives a 1-point answer to B25, say "that's correct, (*fill in his/her 1 point response*) but they are also both body parts or limbs". Record a score of 1.
2. If the participant gives a 0 point answer to B25, say, "They are both body parts or limbs". Record a score of 0.

Body part, limb, etc.	2
Appendages, extremities or extensions of body	2
Part of the anatomy	2
Both have joints, both are used for movement	1
Arm and leg have 3 letters	1
Part of an animal	1
Both are necessary and useful	1
Both bend	1
Two long bones	1
Both dangle	1
All humans/animals have both	0
Have fingers and toes	0

3. If a response is too vague (e.g. "both are useful""", probe and ask the participant to tell you more.

2.F.10.b Q15b Laughing & Crying

Feeling, emotions, inner state	2
Human activities, involve the face (makes your face move)	1
Laughing sounds like crying	1
Both are reactions	1
Both can produce tears	1
Mood	1
Make a noise	1
They are spontaneous	1
Expressions	1
Use vocal chords, voice, eyes	1
Both sound alike = ambiguous.	0

(Probe and ask the participant to tell you more about the response. You have to do them.)

Things that you do in response to other people	0
They're opposites	0
One's happy and one's sad	0

2.F.10.c Q15c Eating & Breathing

Essential, necessary for life, must do both to live, etc.	2
Actions, human/animal activities, help us to live, use your mouth for both everyday activities	1
Involve use of energy	1
You are taking in with both	1
Use oxygen for both	1
Swallow	1
You have to eat to breathe	1
I eat while I breathe = ambiguous.	0
(Probe and ask the participant to tell you more about the response. They are not alike)	
Activities that make you happy	0

2.F.10.d Q15d Repetition

1. Read each sentence aloud. Pronounce the individual words clearly but with normal tempo of a spoken sentence – without artificial slowing and pausing after each word.
2. The sentences need to be repeated *exactly*. If participant did not hear correctly or seems confused, repeat instructions and sentence.
3. Allow for 1 additional repetition of the sentence (Maximum of two trials). Score the best response.
4. If the participant has memory difficulties and repeats a portion of the sentence, repeat instructions and the sentence. Have them repeat the entire sentence. Score the second attempt.

**Abbreviations*: *A check mark in the space to indicate a correct response is acceptable, however, you must record the full sentence/response if it is incorrect.*

2.F.10.e Q15e No Ifs, Ands, or Buts

1. A common error is to leave off the s's. Be sure the s's are emphasized in your articulation.
2. Emphasize to the participant that (s)he is to repeat to your "exactly".
3. Again, you may allow for 1 additional repetition (maximum of two trials).

**Abbreviations*: *A check mark in the space to indicate a correct response is acceptable, however, you must record the full sentence/response if it is incorrect.*

2.F.10.f Q15f-g Commands

The original 3MS had commands using visual items. These have been revised to oral commands.

Q15f Tapping the Phone

1. State the command. If the respondent makes no response within five seconds or indicates that he/she didn't hear you, prompt by repeating the command. Allow another five seconds for a response. Do not paraphrase the command, but state exactly as written.

Q15g Three-Stage Command

1. Similar to B30, repeat the command only once if needed. Do not break up the three steps of the command into three individual commands, but read the entire three-step command for administration.
2. For participants with touch tone phones, it may be difficult to tell if the subject pushed the number one instead of some other number. Don't worry about what number they push; score as correct if they push any button.

2.F.10.g Q15h Sentence

1. Allow ten seconds for a response. Record the sentence verbatim.
2. If the participant doesn't respond or seems confused, provided the prompt, "A sentence has to express a complete thought and has a subject and a verb". Also provided the prompt if the participant provides a phrase that does not include a subject and a verb or that does not express a complete thought (e.g. "Running into the fence…" or "You have a…uh…I forget…").
3. Scoring:

A. A complete sentence with no grammatical errors is scored a 5.

B. A sentence with errors without a prompt is scored a 4 (e.g. has a subject and verb [either stated or implied] and expresses a complete thought, but has grammatical errors such as "She home today", or "You nice".

C. A correct sentence after the prompt receives a score of 3.

D. A sentence with errors after the prompt is scored a 2 and follows the same rules described in B above.

E. An incomplete sentence after the prompt either has a subject or verb missing, or does not express a complete thought.

4. The subject of the sentence can be implied and need not be stated explicitly. For example, the sentence "Have a good day", is complete and "you" would be the implied subject of the sentence. However, a one word greeting such as "Hello" or "Goodbye" would not be considered a complete sentence and should be prompted with the standard prompt.
5. If you are uncertain, record the sentence verbatim and prompt to request another.

**Abbreviations: NA*

2.F.11 Q16 Visual-Spatial ability

1. Be certain to ask the participant not to look at a clock.
2. The participant should imagine that he/she is facing the clock so for the right or left questions, the directions refer to his or her right or left.
3. Note in the introductory example that the big hand is not pointing to either the right or left sides of the clock. You will tell the respondent in this situation that the big hand is pointing to the top of the clock face. The example is similar to Item A (7:00). Although the big hand is not scored in Item A, be certain to record the response in the blank provided.
4. If the respondent misses all items on Item A, discontinue and assign a score of zero to Items B and C.
5. For items B and C, state the items verbatim. Do not paraphrase the items to "eight twenty" or "eleven ten". If the respondent asks for clarification about the time on the clock, you may repeat the time.

2.F.12 Q17 Recall of 3 Words

Prompt as appropriate (see Q11).

*2.G **Additional Administration Notes:***

1. Record any significant sensory limitations, unusual responses, or other significant behaviors. Please be concise in your descriptions.
2. Completion and Protocol Codes are to be assigned after the administration of the T-3MS.

*2.H **Completion codes***

The Completion Code reflects whether or not the T-3MS was completed and, if so, whether or not the participant had physical impairments. If the T-3MS was not completed, you are to use your judgment to indicate the reason. Completion Codes are as follows:

1 = Complete (No sensory or motor impairments)
Use this code when the participant had no sensory or motor impairments. Do not code a 1 if the participant appeared to have any difficulty hearing instructions or items even if no points were missed.

2 = Complete (with physical impairments)
The sensory or motor impairments should be relevant to the activity required by the test. In this case, if the participant has a hearing impairment, code this as 2 as this is clearly relevant to taking the test. Note that you must specify the impairment in the comment field. Other physical impairments may be undetectable in a telephone interview and most likely will not be relevant to the testing.

3 = Break-off (physical)
Use code 3 when either you or the participant breaks off testing because of the impact of physical impairments. An example would be an extremely deaf individual who broke off out of frustration.

4 = Break-off (cognitive)
Use code 4 when either you or the participant breaks off testing because of the participant's cognitive impairment. An example would be someone who after experiencing difficulty, refuses to complete the test because of frustration.

5 = Cognitively untestable
Use code 5 when you were unable to get a response on the first several items because of a lack of comprehension. This code is appropriate when a participant cannot be tested (or interviewed) because of significant cognitive impairment and confusion.

6 = Refused
Participant refused the entire test--no items were attempted. If even one item was attempted, then one of the break-off codes would be more appropriate.

7= Other
This code is assigned when the status of the T-3MS completion does not fit into any of the other coded categories. An example would be if the subject discontinued the test for reasons other than 4 or 5 above, such as poor effort, disinterest or lack of cooperation. This code may be used for any other unusual circumstances as well (e.g. page missing from the booklet).

2.I Protocol codes

Protocol codes help us to track when either non-standardized administration procedures were used or when interruptions occurred during testing. Protocol codes are as follows:

1 = Standard protocol was followed

2 = Non-standard administration procedure(s) was/were used
Use this code if there was any interruption in testing, paraphrasing of instructions due to hearing impairment, or other modifications to facilitate testing.

3 = Not applicable
This code is the appropriate code to use when the completion code is either a 5 or a 7 (untestable or refused).

2.J Impairment of IMp codes

These codes help us to determine the influence of sensory or motor impairments on the participant's test score. These codes are critical to fill out accurately as adjustments to the total T-3MS score will be made for those participants with significant impairments.

Each item has an "IMP" field in which you are to record the presence of any sensory or motor impairment that affected the participant's score for that item. If the person has a sensory impairment (e.g. hearing) but did not miss any points for the item, do not record an IMP code for that item. There is a unique code for vision impairment (1), hearing impairment (2), motor impairment involving the hands (3), or other (4). Only fill in one of these codes (1 - 4) if, in your judgment, the participant's physical impairment interfered to the extent that their score on the item is invalid.

An example of an appropriate use of the IMP Code is:

- INTERVIEWER: Please repeat what I say exactly, No ifsss, andss, or butsss.
- PARTICIPANT WITH HEARING PROBLEM: No if ants or but.
- INTERVIEWER: Let's try it again. No ifssss, andsss, or butsss.
- PARTICIPANT WITH HEARING PROBLEM: No if ants or buts?

Here the code in the IMP field would be 2 to reflect a confound of hearing impairment.

An example of an inappropriate use of the IMP Code is:

- INTERVIEWER: What were the three words that I asked you to remember?
- SAME PARTICIPANT: What three words? I didn't hear any three words.
- INTERVIEWER: Well, perhaps you didn't hear me ask you to remember the three words I showed you on the card.

In this example, the interviewer is trying to help the participant out by attributing their memory problem to their hearing impairment. This is an improper use of the IMP code.

Often times it is difficult to judge whether a participant's difficulty answering a test item is due to cognitive or sensory/motor impairments. In these situations, you will have to rely upon your judgment and observations of the participant. In unclear situations, discuss the case with your supervisor.

2.K Scoring the t-3ms

Complete the scoring box on the Modified Mini-Mental State Exam Phone Tally Sheet (MMMSE_TALLY_PC):

1. Total the score for each page and record in the appropriate box on the last page.
2. Calculate the grand total.
3. Use the decision rules below the scoring grid to determine whether you will continue the interview with the participant.

The T-3MS cut-points for informed consent and, therefore, a Participant Interview, are

- a total score of 60 or above OR
- an Orientation score of 15 or above (out of 20 points).

If the participant's total score falls below 60 or has an Orientation score below 15, then it is unlikely that the participant fully understood the informed consent form or that they will be able to complete the rest of the interview with valid responses.

There may be exceptions to the above where you must use your judgment. There may be participants who score *above* the cut-point but it is apparent to you that they do not adequately understand the study procedures or questions to continue. In this situation, you should not complete the interview with them.

There also may be participants who score below the cut-point because of sensory/motor impairment, anxiety, etc. In this situation, use your judgment about whether or not to administer the interview with the participant.

2.L Summary of Decision Rules

1. If the Total Score for the T-3MS is 60 or higher, proceed with the interview.
2. If the Total Score for the 3MS is below 60 or the Orientation score (See Section 2.F.7.) is less than 15, , record the situation and proceed as you feel appropriate. Discuss the situation later with your PI.

3 SF-12v2™ Health Survey (SF-12v2™)

The SF-12v2™ Health Survey (SF-12v2™) is self-administered to the adult participants during the outpatient, in-person visits. This form is not completed by the pediatric participants. This form takes about two minutes to complete and is written at an eighth grade reading level.

The survey was developed as an alternative to the SF-36 for use in large surveys of general and specific populations as well as larger longitudinal studies of health outcomes. It is a 12-item subset of the SF-36v2™ that measures the same eight domains of health and is intended to be a brief, reliable measure of overall health status. One to two items from each of the eight health concepts in the SF-36 were selected to represent: What the respondent is able to do, How he feels in terms of distress and well-being, How his preparation in his everyday life is affected, and how he personally evaluates his health status.

Question 1:	General Health
Question 2a, 2b:	Physical Functioning
Question 3a, 3b:	Role Physical
Question 4a, 4b:	Role Emotional
Question 5:	Bodily Pain
Question 6a, 6c:	Mental Health
Question 6b:	Vitality
Question 7:	Social Functioning

Offer the self-administered survey to the participant. Ask the participant to read the instructions and answer the seven questions. Place the participant's label on the survey AFTER the participant has completed the survey.

4 TRAILS B

TRAILS B is to be administered at the 3-, 12-, 24-, and 36-month, adult, in-person visits and prior to the Modified Mini-Mental Status Examination (3MS) if applicable. It offers an assessment of cognitive function with the sensitivity for detecting cognitive dysfunction and it is brief. TRAILS B is not administered to the pediatric participants. TRAILS A is not administered.

The Reasons for Missing TRAILS B spreadsheets can be found on the ASSESS website under Committees : Coordinators : Reasons for Missing TRAILS B, and the coordinator has access only to its site's spreadsheet. Refer to the Document Management MOP, Section 2 for more information on how to fill out the spreadsheet. There are also instructions in the Reasons for Missing TRAILS B folder under "How to Fill Out Missing TRAILS B Sheet."

Hand the participant the "Trails B Sample" sheet and a pencil with an eraser.

Script: "On this page are some numbers and letters. Begin at number 1 *(point to 1)* and draw a line to A *(point to A)*, A to 2 *(point to 2)*, 2 to B *(point to B)*, B to 3 *(point to 3)*, 3 to C *(point to C)*, and so on in order, until you reach the end *(point to the circle marked "end")*. Remember, first you have a number *(point to 1)*, then a letter *(point to A)*, then a number *(point to 2)*, then a letter *(point to B)*, and so on. Draw the lines as fast as you can. Ready? Begin."

If the participant makes a mistake point out the error and explain it. If necessary guide the participant's hand through the trail eraser end down. They say "Now you try it," and repeat the original directions starting with "Begin at number 1…" Repeat instructions with guidance twice.

If the participant completed the sample item correctly and shows that s/he understands the task say "Good! Let's try the next one". If the participant still does not understand, terminate Trails B task.

Hand the participant the "Trails B" form. Say, "On this page are some numbers and letters. Do this the same way. Begin at number 1 *(point to 1)* and draw a line to A *(point to A)*, A to 2 *(point to 2)*, 2 to B *(point to B)*, B to 3 *(point to 3)*, 3 to C *(point to C)*, and so on in order, until you reach the end *(point to the circle marked "end")*. Remember, first you have a number *(point to 1)*, then a letter *(point to A)*, then a number *(point to 2)*, then a letter *(point to B)*, and so on. Draw the lines as fast as you can. Ready? Begin."

Start timing as soon as the instruction is given to begin. Allow a maximum of 300 seconds (5 minutes) for the task. WATCH CLOSELY IN ORDER TO CATCH ANY ERRORS AS SOON AS THEY ARE MADE. If the participant makes an error, identify it immediately, draw a perpendicular line through the incorrect line and tell them to proceed from the number where the mistake occurred. DO NOT STOP TIMING. If the participant goes over 300 seconds (5 minutes), stop the test.

4.A Scoring Instructions

Record the number of years of school the participant has completed in Q1000. The maximum number of years this field currently allows is 22. If the participant reports a number of years greater than 22, enter 22 in Q1000 and add a comment in Q6000 with the actual number of years reported.

Record the start time, end time, and total amount of time the participant took to finish the Trails B task on TRAILSB_SCORE form.

See Appendix C for sample of TRAILS B form

5 PedsQL™ Administration Guidelines℠

The following guidelines are intended for use by individuals trained in the administration of standardized questionnaires. The PedsQL™ administrator is crucial in developing rapport with the respondents, emphasizing the importance of the questionnaire, addressing concerns, and ensuring that the PedsQL™ is completed accurately and confidentially.

5.A General Protocol

1. Create a procedure for assigning identification numbers that will allow for parent/child comparisons as well as comparisons of baseline/follow-up data.
2. If feasible, the PedsQL™ should be completed *before* the respondents complete any other health data forms and *before* they see their physician or healthcare provider.
3. The parent/child should first complete the PedsQL™ Generic Core Scales and then complete any additional PedsQL™ Module.
4. Parents, Children (8-12) and Teens (13-18) may self-administer the PedsQL™ after introductory instructions from the administrator. If the administrator determines that the child or teen is unable to self-administer the PedsQL™ (e.g., due to illness, fatigue, reading difficulties), the PedsQL™ should be read aloud to the child or teen. For the Young Child (5-7), the PedsQL™ should be administered by reading the instructions and each item to the young child word for word. At the beginning of each subscale repeat the recall interval instructions (one month or 7 days) to remind the young child to respond only for that specific recall interval. Use the separate page with the three faces response choices to help the young child understand how to answer. When reading items aloud to a child, intonation should be kept neutral to avoid suggesting an answer.
5. If a child has difficulty understanding the age-appropriate PedsQL™, the preceding age group version may be administered to the child (e.g., administering the Young Child (5-7) Self-Report version with the three faces response choices to an 8 year old). However, if a child presents with severe cognitive impairments (as determined by the administrator), the PedsQL™ may not be appropriate for that child. In such cases, only the Parent-Proxy Report should be administered to the child's parent.
6. The parent and child must complete the questionnaires *independently* of one another. Discourage the parent, child, or other family members from consulting with one another during the completion of the questionnaire. Let them know that they can feel free to discuss their answers following completion of the questionnaires, but that it is important to get both the parent's and the child's *individual* perspectives. If you are administering the questionnaire to the child, the child should be facing away from the parent.
7. If the child or parent has a question about what an item means or how they should answer it, do not interpret the question for them. Repeat the item to them verbatim. Ask them to answer the item

according to what *they think the question means*. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. The child and/or the parent has the option of not answering a question if they truly do not understand the question.

8. If a parent/child asks you to interpret the responses, tell her/him that you are not trained to interpret or provide a score for the answers given. If the PedsQL™ is being used for a clinical study, let the parent/child know that their answers will be combined with other participants' answers and analyzed as a group rather than as individual respondents.
9. Document all reasons for refusals and non-completions of the PedsQL™.

5.B Administering the PedsQL™

1. The following scripts have been developed as a guide to introduce the PedsQL™ to the child and his/her parent(s). Modify the language to a style that is most appropriate for you and the respondent.

For the child:

The PedsQL™ asks you questions about how you feel and what you think about your health. It is not a test, and there are no right or wrong answers. It takes about 5 minutes to complete. If you have any questions, please let me know.

For the parent:

The PedsQL™ is a questionnaire that assesses health-related quality of life in children and adolescents. It contains questions about your child's physical, emotional, social, and school functioning in the past one month *(or for the Acute version,* in the past 7 days*).*

The PedsQL™ is brief and typically takes less than 5 minutes to complete. It is not a test, and there are no right or wrong answers. Please be sure to read the instructions carefully and choose the response that is the closest to how you truly feel. Please do not compare your answers with your child's responses. We are interested in your and your child's individual perspectives. However, feel free to discuss the questionnaire with your child after you have both completed it and returned it to me. If you have any questions, please let me know.

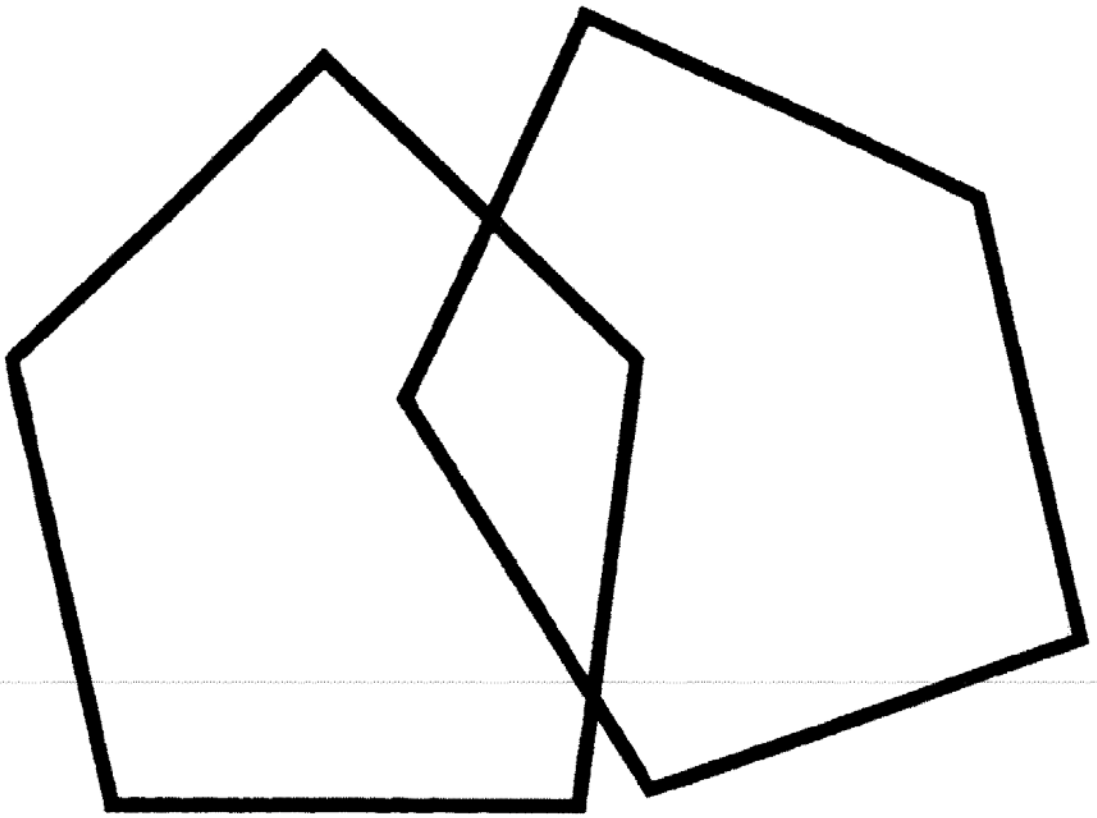
2. Provide the respondent with a pen or pencil and a solid writing surface. If a table is not available, the participant should be provided with an item such as a clipboard. Remain nearby should questions or concerns arise.
3. When the parent/child returns the PedsQL™, look it over and check to see that all answers have been completed. Verify that no item has more than one response. If any responses are incomplete, illegible, or there are multiple responses for an item, please ask the parent or child to indicate their response.
4. Ask the participants if they had any difficulties completing the questionnaire or if they have any other comments regarding the questionnaire. Document any important feedback.

5. Thank the parent and child for taking the time to complete the questionnaire. If the study design involves following up with these respondents, let them know that they may be asked to complete the PedsQL™ again at another time. Indicate when they can expect to be contacted again if known.

6 APPENDIX A

CLOSE YOUR EYES

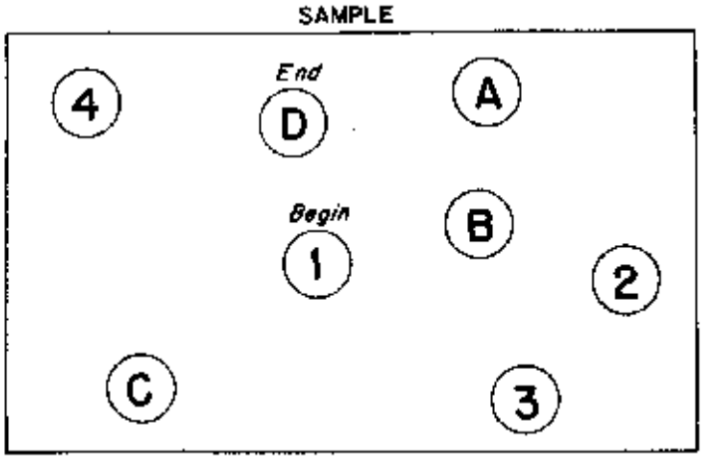
7 APPENDIX B

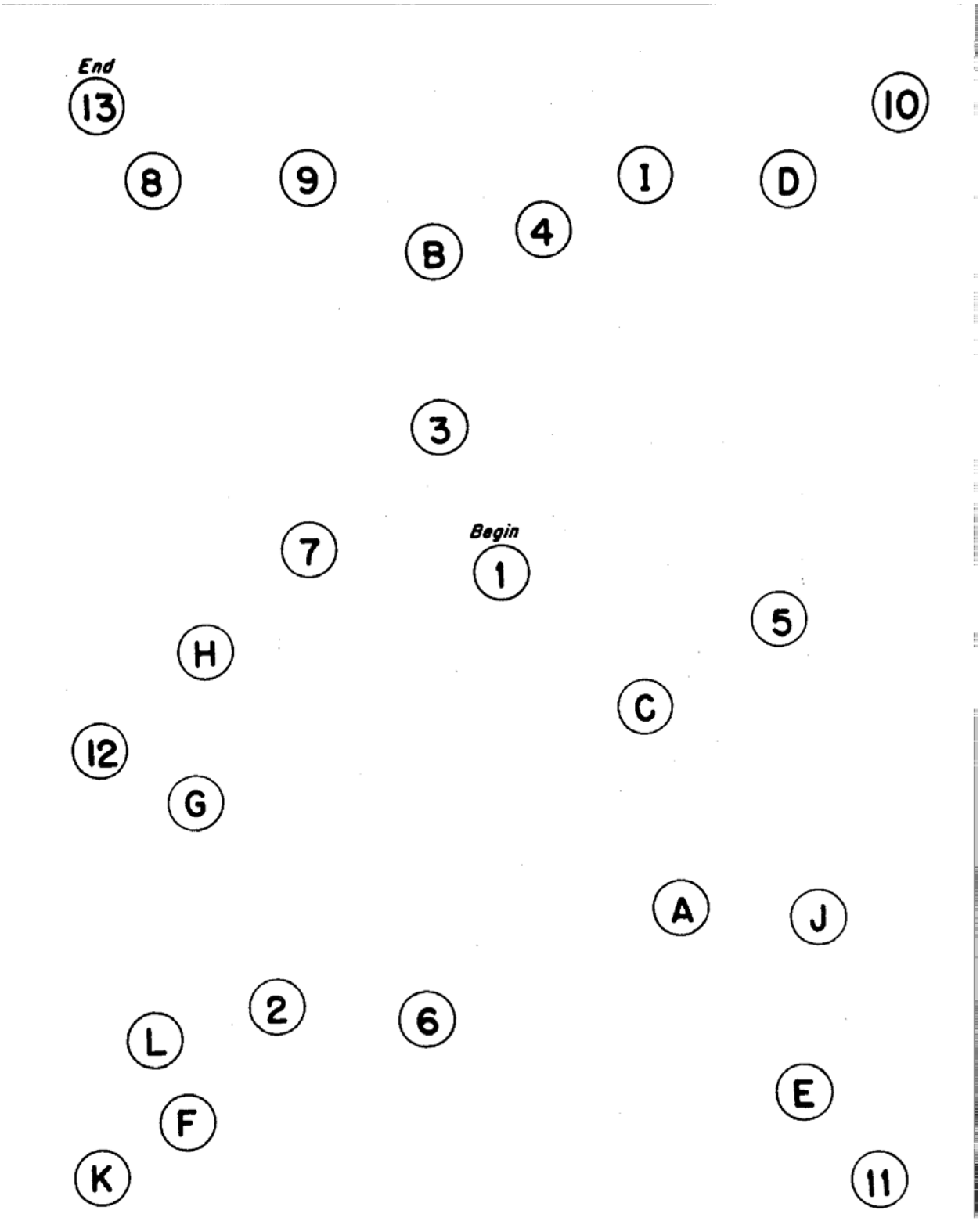


8 APPENDIX C

TRAIL MAKING

Part B




End
13
10
8
9
1
D
4
B
3
7
Begin
1
5
H
C
12
G
A
J
2
6
L
E
F
K
11

Electrocardiography Assessment Manual

The ASSESS-AKI Study

Prepared by

ASSESS-AKI Central ECG Reading Center (CERC)

Epidemiological Cardiology Research Center (EPICARE)
Department of Epidemiology and Prevention Division of Public Health Sciences
Wake Forest University School of Medicine

Elsayed Soliman MD, MSc, MS January 26, 2010

TABLE OF CONTENTS

I. INTRODUCTION

The ASSESS-AKI Central ECG Reading Center (CERC), EPICARE, is located at Wake Forest University Health Sciences, Winston Salem, NC.

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II.BACKGROUND AND PURPOSE

The electrocardiogram (ECG) will be recorded in ASSESS-AKI study at the 3-, 12-, 24-, 36-, 48-, 60-, 72-, and 84-month visits.

After October 04, 2016, the following applies to all adult sites.

- Baseline ECG
  - All adult sites should make every effort to obtain an ASSESS-AKI ECG (either through their research center or send the participant to the ECG lab) or retrieve a clinically-obtained ECG from the participant's medical records.
  - For participants who have already completed the V3M visit but in whom research personnel did not obtain a protocol-driven ECG at that time, clinical records from the site should be reviewed and a clinical ECG most proximate and preceding the V3M visit should be obtained. This ECG could be obtained during the V0 hospitalization or at an outpatient visit or during a hospitalization that is not more than 365 days prior to the V0 hospitalization. Preferably, an ECG nearest to the V0 hospital discharge date would be available and would be acceptable.
  - Baseline ECG is defined as an ASSESS-AKI ECG at V3M, a non-ASSESS ECG obtained during the V0 hospitalization, or at an outpatient visit or hospitalization that is no more than 365 days prior to the V0 hospitalization.
  - Baseline ECGs should be obtained for those who withdraw at or after V3M without a post-baseline ECG.
  - Baseline ECGs should be obtained for those who withdraw at or before V24M without a post-baseline ECG.

- Post-Baseline ECG
  - In-center visits – all adult sites should obtain an ASSESS-AKI ECG for all visits (either through their research center or send the participant to the ECG lab), or retrieve a clinically-obtained ECG from the medical records within the follow-up window in each study year.
  - Home visits/Phone visits in lieu of in-center visits - all adult sites should attempt to obtain mobile 12-lead ECG. If a mobile 12-lead ECG is not possible, the coordinator will know after the next phone contact if there was a hospitalization(s) or ER visit (P1_EVENTS, Q1000 = 1) and will ask if s/he has received a 12-lead ECG during the hospitalization or within the last six months. If the participant does not know if an ECG was completed, a quick search of the local EMR should be completed. After completing the HOSP_EVAL for the hospitalization(s), the coordinator will request an ECG as part of the medical records request. If an ECG is not available from the medical records, the coordinator shall contact the provider where an ECG was completed within the last six months; this can be a hospital, clinic, or physician office. If no healthcare visits occurred in the prior six months, the ECG will be considered missing.
  - Post-baseline visit ECG is defined as any ECG (ASSESS or non-ASSESS) obtained after V3M.

- Only one ECG should be obtained annually after the post-baseline ECG, and it should be collected at the annual visit or a hospitalization most proximate after the scheduled visit.

Example #1: V24 ECG is obtained. There is no ECG obtained at V36; no further action is needed at that time. At the next phone call visit, these are possible scenarios.

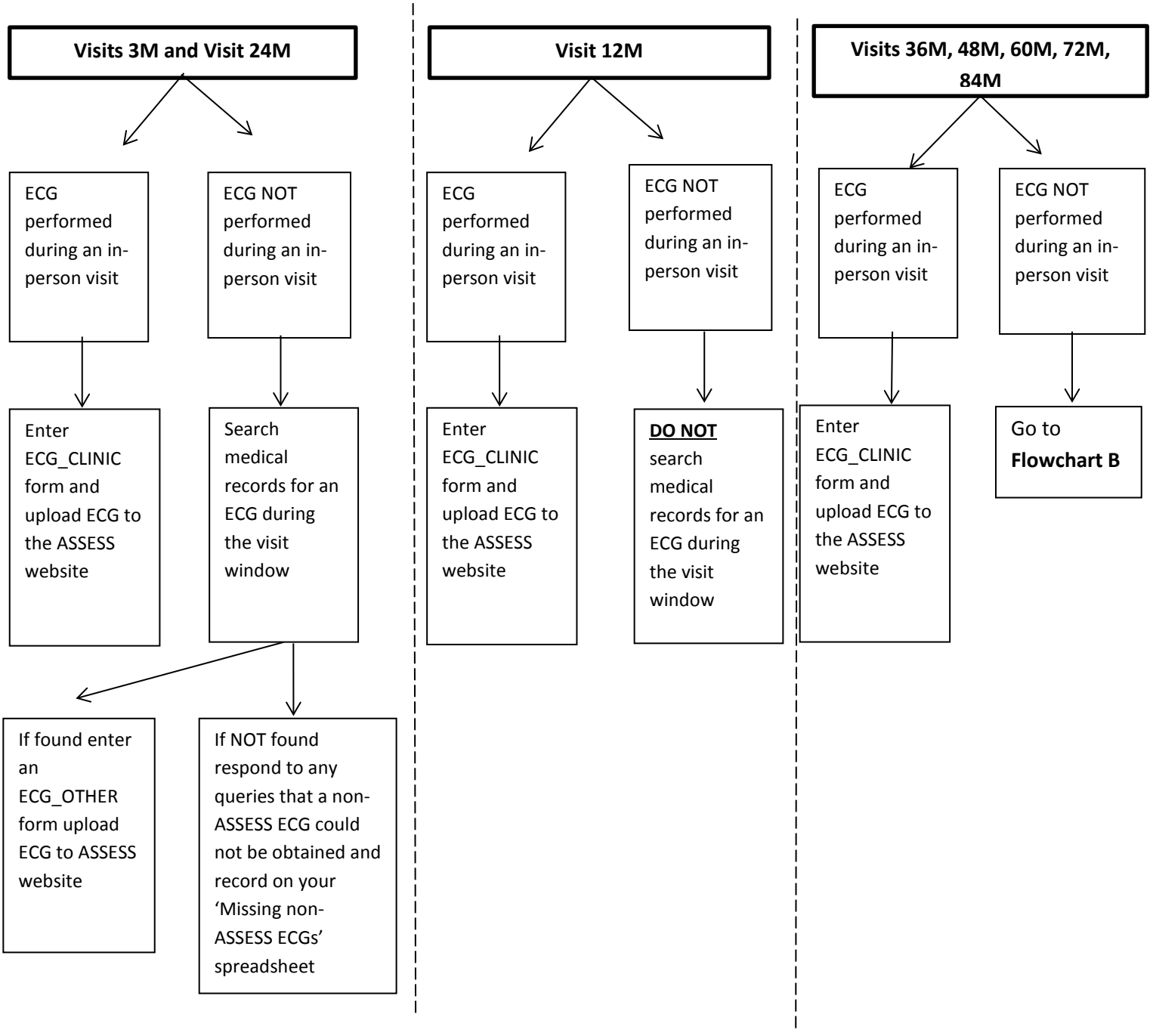
1) At V42 phone call, the participant indicates that s/he was hospitalized. The coordinator asks the participant if an ECG was done during the hospitalization or within the last six months. If an ECG was obtained, the coordinator will try to obtain it from the medical records or provider. If the ECG is available, complete the ECG_OTHER form, data enter the form, and keep the ECG stored at site. If s/he hasn't had an ECG or no ECG is available, no further action is needed.

2) At V42 phone call, the participant indicates that s/he was not hospitalized. The coordinator asks the participant if an ECG was done within the last six months. If yes, the coordinator shall contact the provider where an ECG was completed within the last six months. If the ECG is available, complete the ECG_OTHER form, data enter the form, and keep the ECG stored at site. If s/he hasn't had an ECG or no ECG is available, no further action is needed.

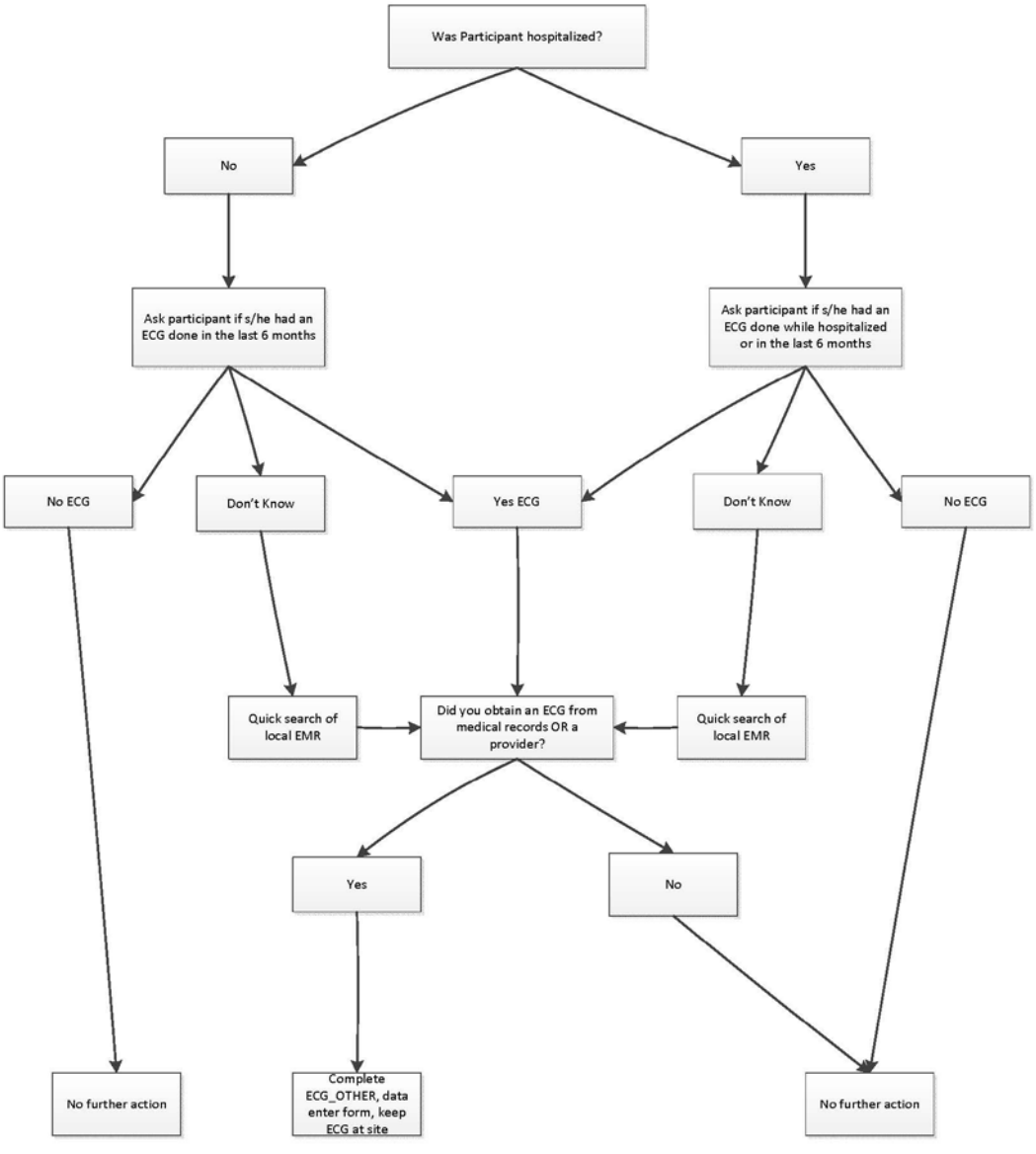
3) If the participant does not know if an ECG was completed, a quick search of the local EMR should be completed.

Example #2: There is no ECG obtained prior to or at V3M. There is an ECG obtained at V36; this becomes the Post-Baseline ECG.

Flow Chart A


Visits 3M and Visit 24M
ECG performed during an in-person visit
ECG NOT performed during an in-person visit
Enter ECG_CLINIC form and upload ECG to the ASSESS website
Search medical records for an ECG during the visit window
If found enter an ECG_OTHER form upload ECG to ASSESS website
If NOT found respond to any queries that a non-ASSESS ECG could not be obtained and record on your 'Missing non-ASSESS ECGs' spreadsheet
Visit 12M
ECG performed during an in-person visit
ECG NOT performed during an in-person visit
Enter ECG_CLINIC form and upload ECG to the ASSESS website
DO NOT search medical records for an ECG during the visit window
Visits 36M, 48M, 60M, 72M, 84M
ECG performed during an in-person visit
ECG NOT performed during an in-person visit
Enter ECG_CLINIC form and upload ECG to the ASSESS website
Go to Flowchart B

Flow Chart B



There also will be some intermittent ECGs for patients who are suspected to experience cardiovascular events. Given that there will be 1200-1300 participants in the study, it is estimated that there will be a total of 4,500 ECGs. ECGs will be scanned and converted into PDF files that are accessible by the ASSESS-AKI CERC (Further details will be provided by the ASSESS-AKI Data Coordinating Center (DCC)). The ECG recording will serve to establish the distribution of cardiac disease findings at baseline and development of new findings in the follow up visits. In this context, the ASSESS-AKI central ECG reading center (ASSESS-AKI CERC), will provide a standardized reading for all ECGs for establishing ECG abnormalities including myocardial infarction, myocardial ischemia, left ventricular hypertrophy, prolonged QT interval and arrhythmias as well as the development of subclinical ECG findings that are determined to be associated with a poor prognosis. Minnesota ECG classification will be the basis for the standardized reading.

III. FIELD CENTER PROCEDURES

The field center procedures include ECG acquisition, sending the ECG records to the CC/ECG center (as will be directed by the study CC), and local ECG reading by the clinic physician if necessary.

III.1. ECG acquisition

Each participant will have one resting 12-lead ECG recording.

III.1.1 Equipment and supplies needed for recording

Table 1 summarizes the equipment and supplies needed for recording and transmitting ECGs.

Table 1

Equipment	Supplies (always order in advance)
• Electrocardiograph • HEARTSQUARE • Scissors • Felt tip non-toxic washable markers • The CERC contact list (Appendix A)	• ECG paper • Disposable silver chloride electrodes • Alcohol swabs and gauze pads • Cotton surgical tape • Examining table disposable paper

III.1.2 Preparation for ECG recording

Prior to electrode placement, there are some steps and precautions to be followed:

- Participant should be relaxed and comfortable in supine or semi-recumbent position.
- Examination table/bed should be adequate to comfortably accommodate the participant. Supply drape for exposed upper torso. An additional covering may be needed to prevent the participant from becoming chilled.
- Make sure ankles and wrists are accessible for electrode application.
- ECG electrode placement should always be performed with the technician standing to the participant's left side.
- Supplies needed for ECG acquisition should be assembled and arranged efficiently.

III.1.3 Location of the ECG electrodes

III.1.3.1 Location of limb electrodes (Figure 1)

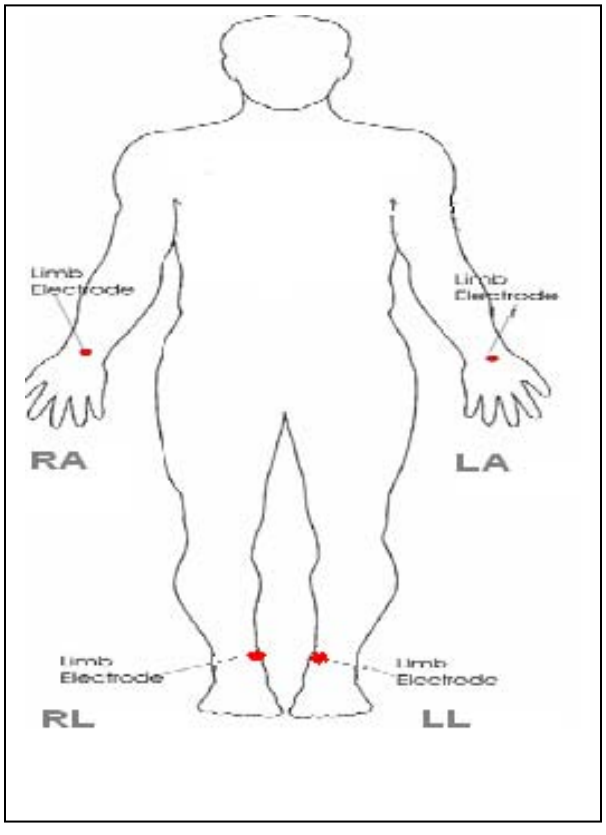
RIGHT LEG (RL) AND LEFT LEG (LL):

- On the inner side of the right leg (RL), above the ankle, rub briskly an area about 1-2 inches in diameter with an alcohol swab using firm, circular motions
- Mark the position to place the electrode later.
- Repeat this procedure for the left leg (LL).
- In amputees, the leg lead electrode may be placed higher up on the torso.

RIGHT ARM (RA) AND LEFT ARM (LA):

- Rub the inner side of the right arm (RA) above the wrist similar to what you did with the right and left legs.
- Mark the position to place the electrode later.
- Repeat the process for the left arm (LA).
- In amputees, the arm electrode may be placed on the shoulder, below the clavicle.

FIGURE 1



III.1.3.2 Location of chest electrodes

V1 AND V2:

- First locate the sternal angle about the width of your 3 middle fingers below the sternal notch (Figure 2).
- Feel the sternal angle between the index and middle fingers of your right hand, keeping the fingers wide apart and moving your fingers firmly up and down. While feeling the sternal angle, move your fingers to the left side of the sternum and feel the 2nd rib between your fingers where it joins the sternal angle.
- Move your middle finger to the interspace below the second rib and with your index finger locate the interspace below the next rib (3rd) and again below the next (4th) rib. This is the 4th intercostals space. Mark an X at this level at the midsternal line. X is the reference level for V1 and V2. Mark their location at the right and left sterna border (Figures 2 and 3).

FIGURE 2

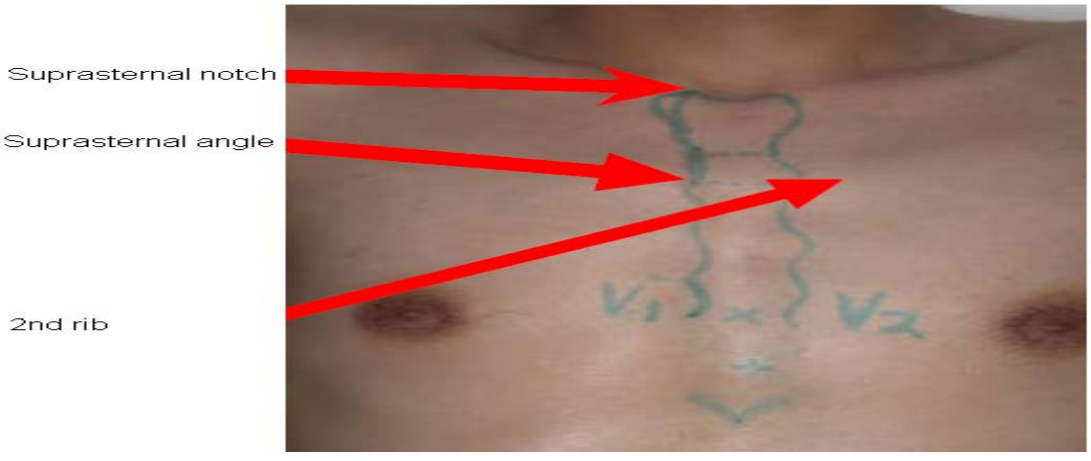
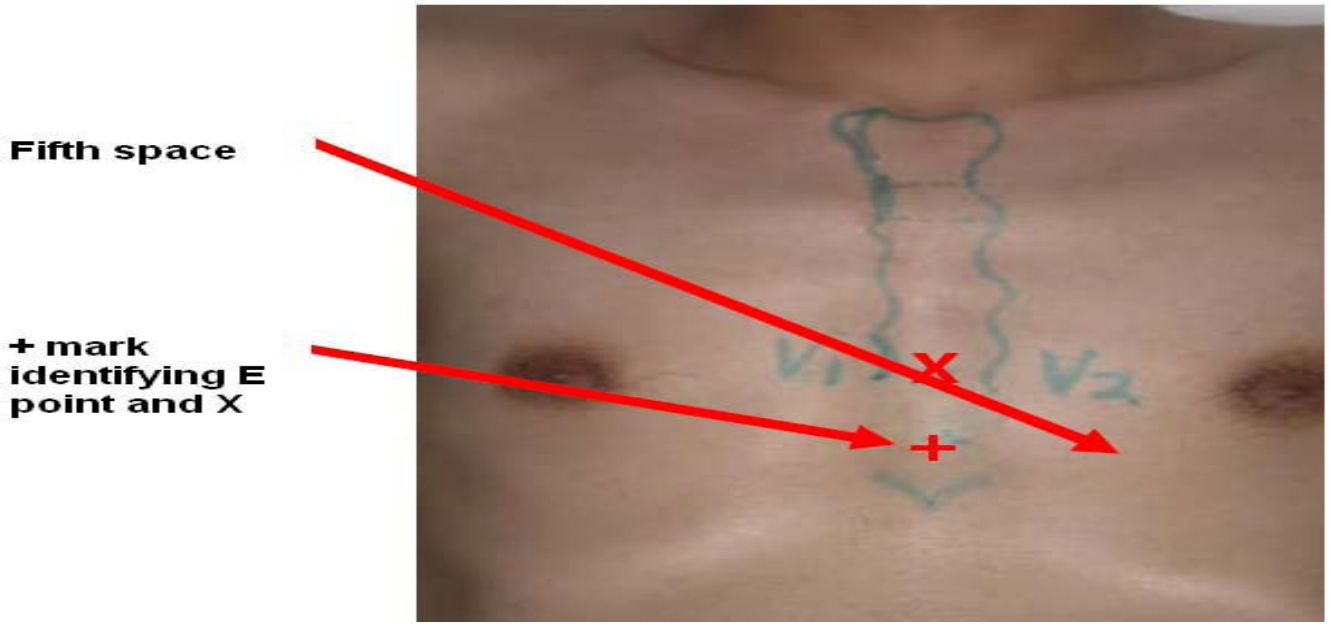


FIGURE 3



- REFERENCE POINT “E” FOR LOCATING V4, V5, AND V6• From the location of V2, palpate with the middle finger of your right hand the intercostalspace and follow it laterally outside the sternal border and at a slight angle down. Feel the 5th rib between your index and middle fingers and feel the 5th intercostal space with 6 your index finger.At the level of the 5th intercostal space, mark a + at the midsternal line below your x mark for V1-V2 level. This + is the reference level “E” for V4, V5, and V6 (Figure3). In overweight persons and in women with tender breast tissue, it is often difficult to locate the 5th intercostal space. In such a case, mark the + for E point 1 ¼ in (3 cm) below your reference level X for V1 and V2 (in smaller adults, 1 inch. (2.5 cm) is enough).

APPROXIMATE LOCATION OF V6

- Move the left elbow laterally without moving it anteriorly or posteriorly, while observing the anterior and posterior axillary folds. The left elbow must be supported properly.
- Follow a line exactly in the vertical midplane of the thorax (mid-axillary line - Figure 4) down where the line meets the horizontal plane of e point. Using your marker, make a vertical one inch long line there as an approximate location of V6.

EXACT LOCATION OF V6

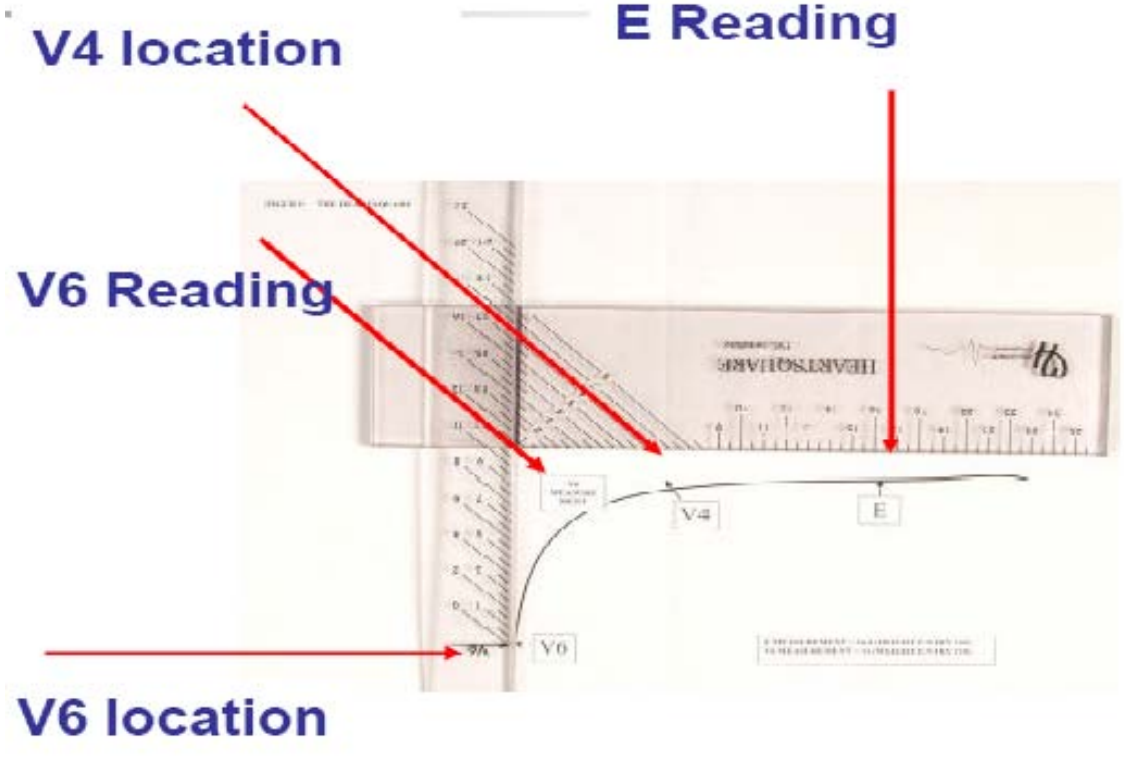
- Exact location of V6 is determined by using the HeartSquare.
- Place the HeartSquare horizontally with the wider arm (E arm) at level e point (Figure 4).
- Slide the V6 arm of the HeartSquare towards the midaxillary line until the arrow points to the mark at the midaxillary line. Mark the exact location of V6 at the level of the arrow on the V6 arm.

FIGURE 4

EXACT LOCATION OF V4

- While keeping the HeartSquare in the horizontal position with the arrow on the V6 arm pointing toward the V6 position, observe the reading at E point. (Figure 5)
- Use this e reading on the centimeter scale on the V6 arm, and follow this same E reading along the 45 degree lines towards the torso to locate the exact position of V4.
- Now that you have located V6 and V4, secure the V6 arm with your thumb to prevent it from sliding. Note the V6 reading which is the distance from the arrow on the V6 arm to where this arm intersects the E arm at right angles. You may then remove the HeartSquare.
- Enter the E and V6 measurements as three digits. Figure 5 shows that the E entry is 160 and the V6 entry is 120 for the readings of 16.0 cm and 12.0 cm, respectively. Further instruction on where to enter these values will be provided later by the ASSESS-AKI CC.

FIGURE 5



LOCATIONS OF V3 AND V5

- Mark V3 exactly halfway between V2 and V4.
- Mark V5 exactly halfway between V4 and V6. (Figure 6)

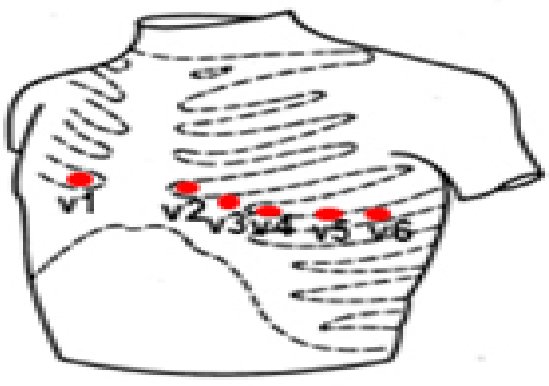


FIGURE 6

III.1.3.3 Attaching the electrodes:

- After you have marked electrodes positions and rubbed them with alcohol swabs, you may apply the electrodes.
- Do not place electrodes directly over bone.
- Attach lead wires in the same, correct order every time to establish routine and to eliminate lead swaps.
- Position the electrodes cables on the participant's abdomen.
- Make sure lead cables have some slack and are hanging loosely.
- You may secure the lead cable to the skin by applying paper tape 1-inch below the clip, especially if the ECG shows baseline noise despite careful preparation.

III.2. Local ECG reading

Because there are no available diagnostic statements from the ECG reading center except as monthly measurement reports to the Coordinating Center and because the diagnostic statements printed on the ECG are not always correct, the local clinic reading of the ECGs is essential for safety purposes. The ECG technician should observe the following in responding to the print out from the ECG:

1) If the ECG machine reading (which is printed on top of the ECG) indicates a normal ECG, sinus arrhythmia, sinus bradycardia (rate >40), sinus tachycardia (<105), axis deviation, PACs, rare PVCs, right bundle branch block, incomplete BBB, first degree AV block, the technician may tell the participant that the ECG "did not have any significant clinical findings, but it will be reviewed by a physician within the next two days."

2) If the ECG machine reading (which is printed on top of the ECG) indicates nonspecific ST-T abnormalities, complete left bundle branch block, non-specific interventricular conduction delay, ventricular preexcitation or Wolf-Parkinson-White (WPW), atrial fibrillation or atrial flutter (if present on previous ECG: if new finding see below), cardiac pacemaker, junctional rhythm, or low voltage QRS, the technician may say, "the ECG does not show any MAJOR abnormality, but it will be reviewed by a physician later today."

3) Certain ECG findings printed on the clinic ECGs need to be reviewed by the clinic physician immediately before the participant leaves the clinic. Technicians need to look for and clinic study physicians need to review and report on "alert" ECGs at baseline or follow-up; i.e., when the printout of a recorded ECG indicates one of the following conditions:

a. Atrial fibrillation – if new since previous ECG (Figure 7)
b. Atrial flutter – if new since previous ECG (Figure 8)
c. Ventricular tachycardia (Figure 9)
d. Ventricular fibrillation
e. Acute myocardial infarction or other acute cardiac ischemic changes (Figure 10)
f. Complete atrioventricular block (Figure 11)
g. Bradycardia with heart rate < 40 beats/minute In the case of any of these alert statements, the tracing should be reviewed by a clinic physician who will decide if any further action is needed. It is not advisable to alarm the participant by revealing these unconfirmed interpretative statements.

However, it is helpful to casually inquire if the person has recently had chest pain or discomfort or shortness of breath. A negative answer does not mean that the alert can be ignored because heart attacks can be asymptomatic (silent). These "asymptomatic alerts" are less urgent than alerts associated with recent potential ischemic or arrhythmia-related symptoms or fainting attacks.

Figure 7. Atrial fibrillation.
Diagnosis key points: irregular QRS complexes (heart rate) and absence of the P wave.

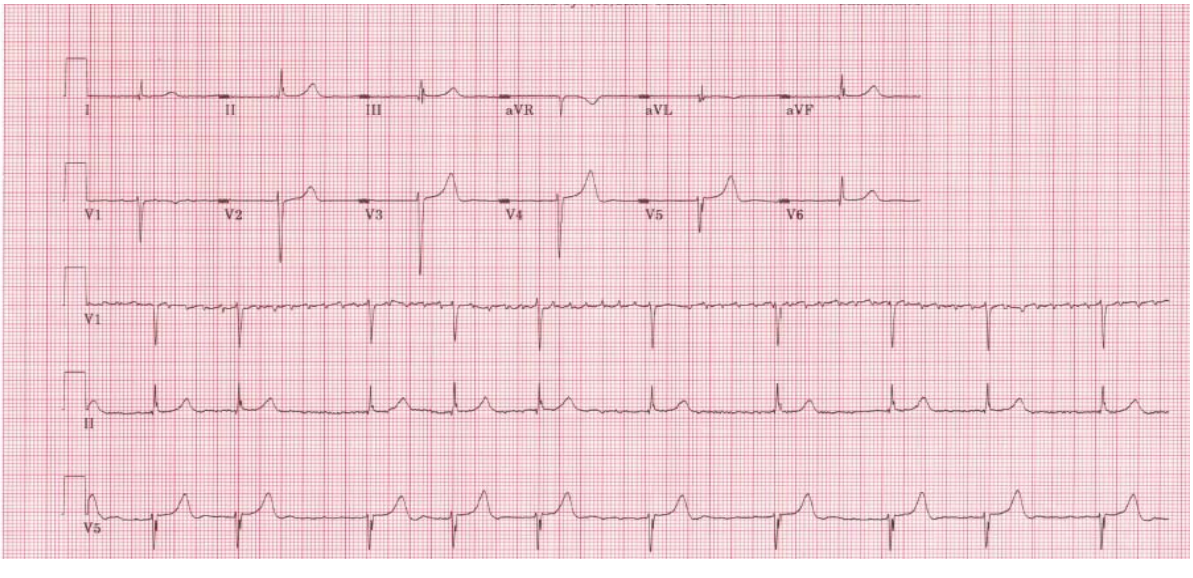


Figure 8. Atrial flutter

Diagnosis key points: multiple P waves; saw-teeth pattern (as in V1), mostly regular but could be irregular with a certain pattern (regular irregularity).

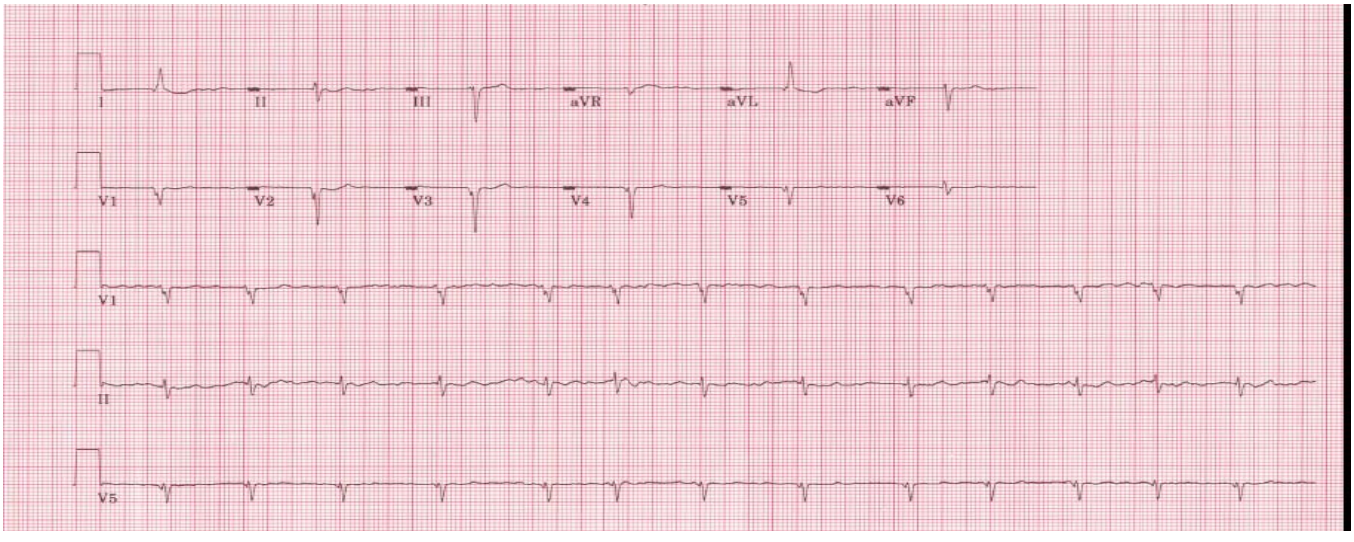


Figure 9. Ventricular tachycardia

Diagnosis key points: Wide complex tachycardia (HR≥110) with QRS not preceded by P wave. The participant will be mostly restless

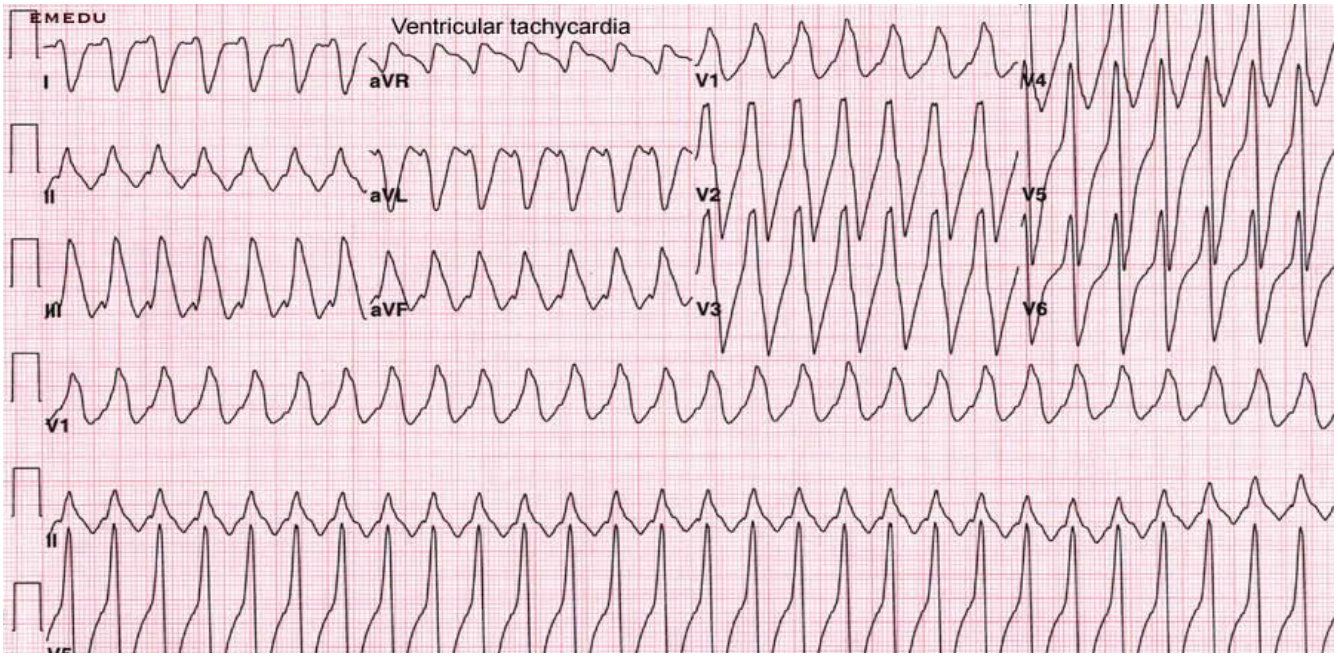


Figure 10. Acute inferior (upper panel) and acute anterior (lower panel) myocardial infarction

Diagnosis key points: Elevated ST segment in a group of adjacent leads with or without Q waves and with or without ST depression in other leads. Patients usually will have chest pain

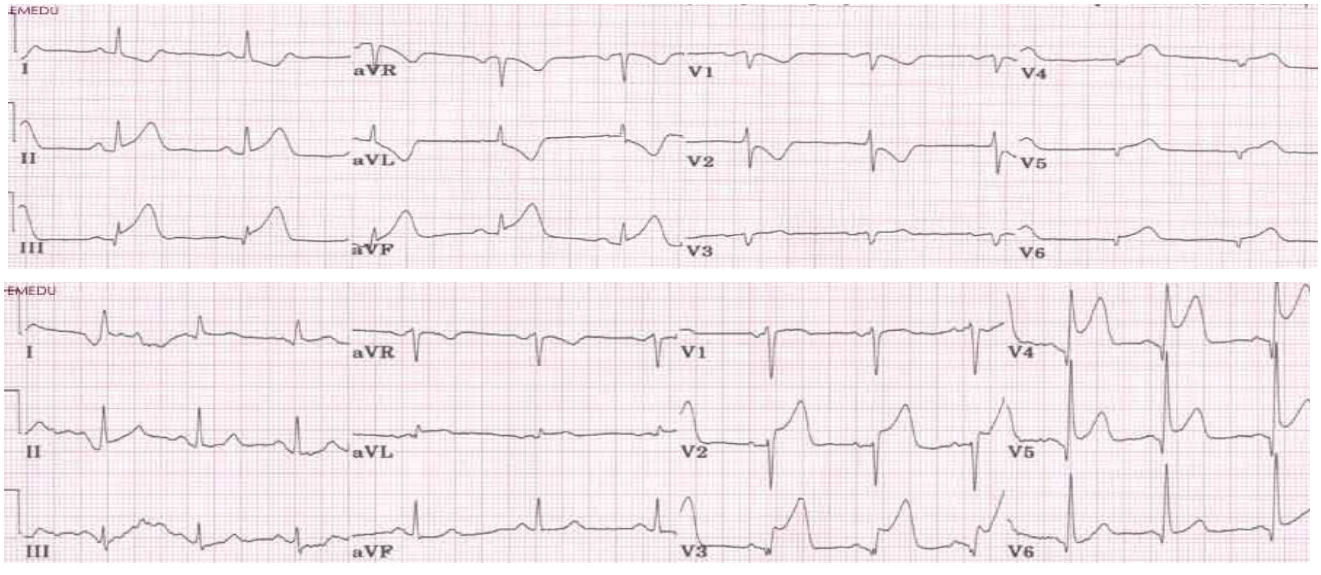
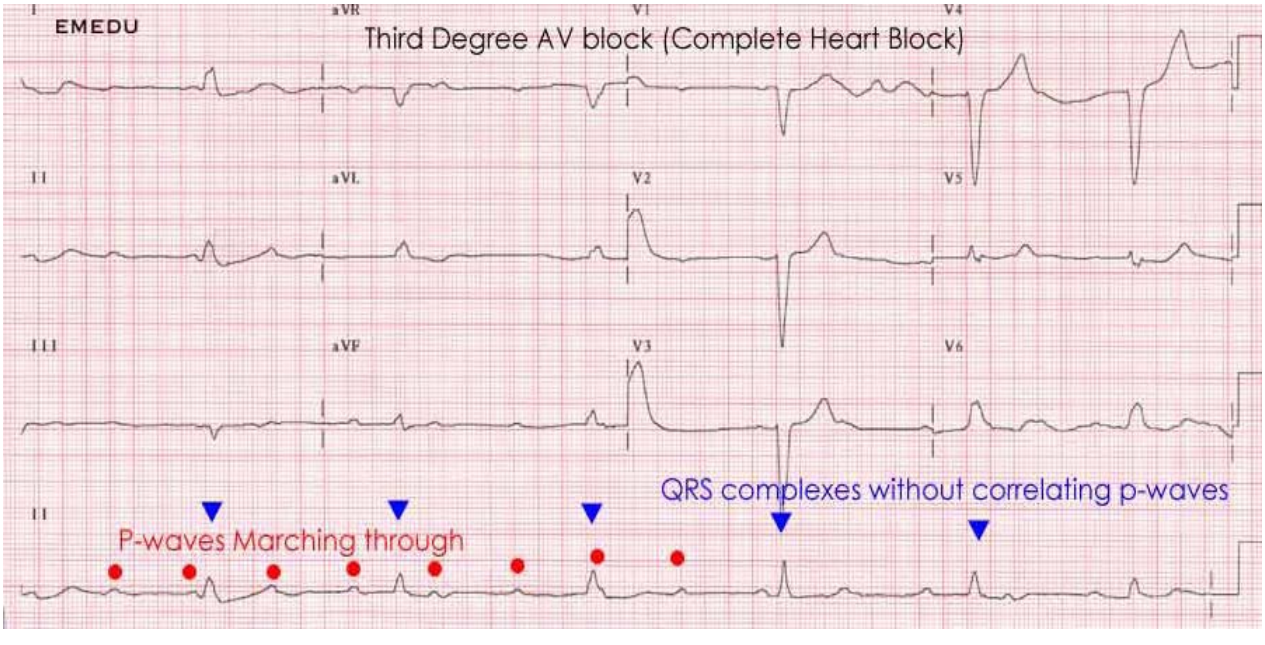


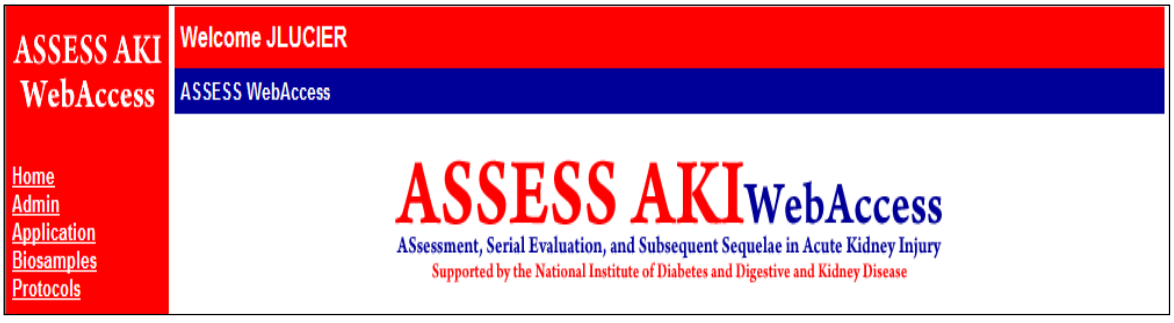
Figure 11. Third degree atrioventricular block.

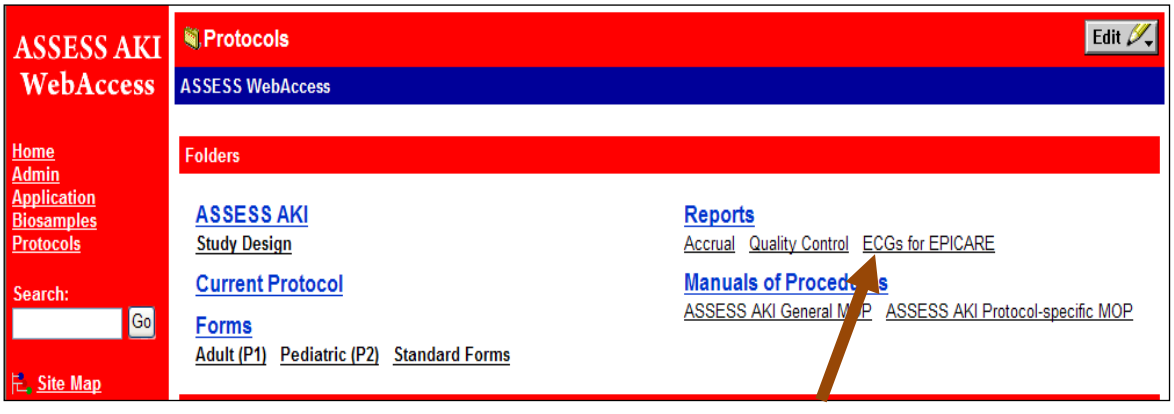
Diagnosis key points: Slow heart rate (around 40 beats per minute) with no relation between the P wave and the QRS

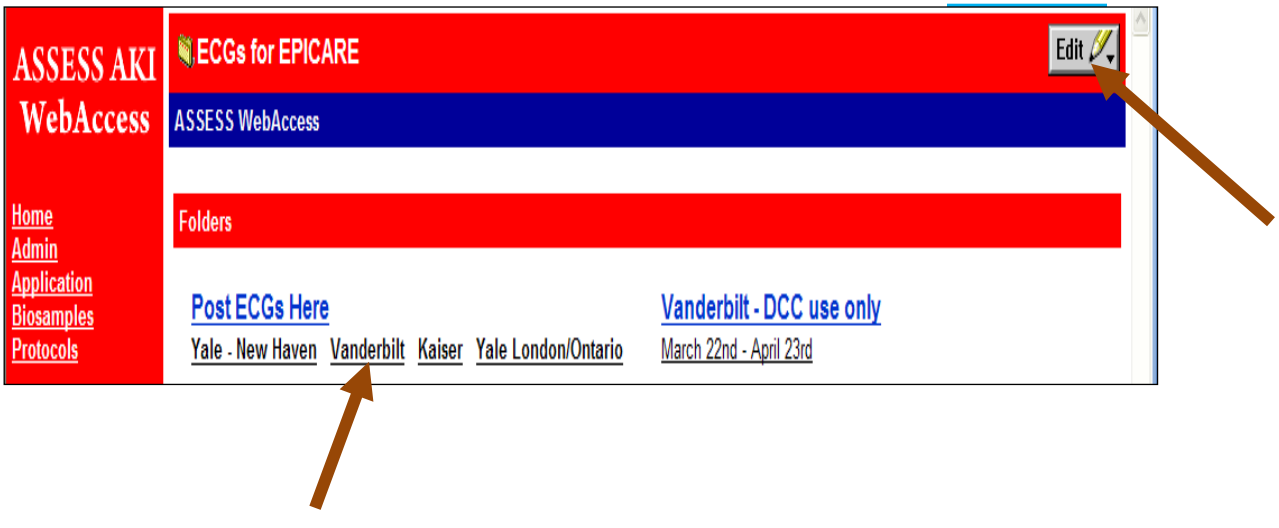


III.3. Data management procedure – ECG_CLINIC

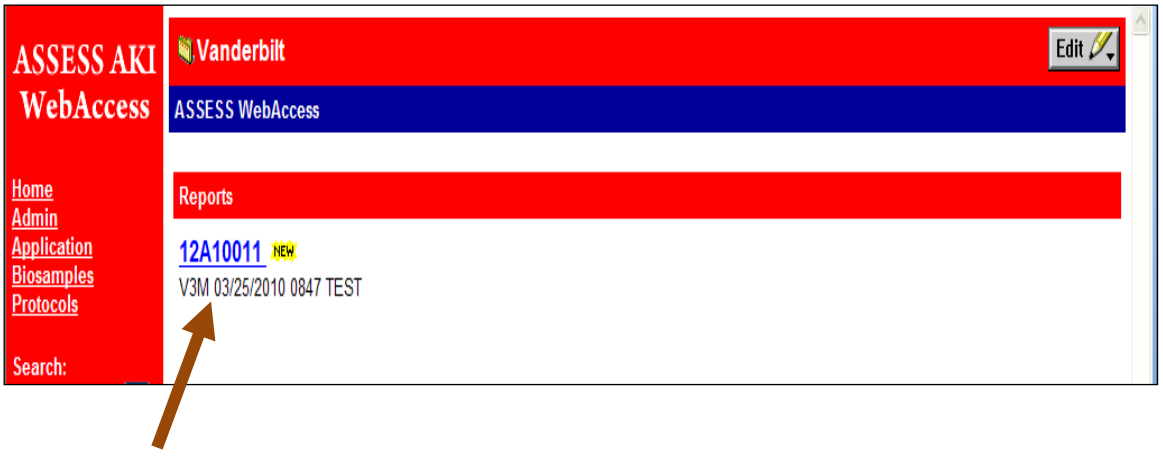
A. Prepare the ECG printout by affixing a label to it.
    1. Label template is located on the website under the 'Forms' folder.
    2. When completing the labels, fill in participant ID and initials only.
        - Type the ID, select the 'Tab' key (Enter key will not work).
        - Type in the Initials, select the tab key.
        - The completed information will populate on all labels on the page.
        - Select 'Print', making sure the Avery 5160 label sheet is in your printer.
        - Label Instructions are also posted on the website with the template.
    3. Keep the sheet of labels in participant folder for QOL, Cognitive Function, or future ECG printouts.
    4. Complete the date, visit number, and CC_ID each time you use a label on a new printout.
    5. Cover participant identifiers, i.e., name, MRN, etc with the label if possible.
    6. If participant identifiers are not covered with the label, blacken these out with a marker.
    7. Examples sent show where we placed the labels for each site, but you can decide what works best for your site.
B. Scan the ECG printout into a folder on your computer
    1. To upload to website you will need to access these files
    2. It would probably be good to set up a folder for each month, but each site can determine the process that works best for them.
    3. Proceed to the ASSESS AKI website:
    4. Protocols
    5. Reports
    6. ECGs for EPICARE
    7. Post ECGs Here
    8. Select your site name
        - Yale – New Haven
        - Vanderbilt
        - Kaiser
        - Yale London/Ontario
        - UW- Harborview







C. Select the 'Edit' link in the upper right corner
D. DCC has added one TEST to each site, as an example to follow.



E. Select the '+' (first icon in each row) to add an item below.
   1. Choose 'file' from the LOV for item type.
      - Select 'Next'
   2. Type the Participant ID, followed by '1', '2', '3', etc. This indicates the first, second, third ECG posted for that participant.
   3. In the description field:
      - Visit Number
      - Visit Date
      - Time of ECG – using 24 hour clock
   4. Do NOT include an expiration date.
   5. Check the box 'Open in a new window'
   6. Select 'Browse' to find your file located on your computer
   7. Select 'Submit'

F. Each site should choose a day that they will upload their reports and perform this weekly.

G. The DCC will pull the ECG reports from the center folders each Friday and place in the 'DCC use only' folder on the website.

H. On the last working day of each month, DCC will batch all of the month's reports.

I. On the first day of the following month, DCC will send the batch of monthly ECG's to EPICARE.

J. EPICARE will provide reports to the DCC on a monthly basis.
   1. Application report will be posted on the website containing the raw data (set up of this report is still being discussed)
   2. Quality control report will also be posted to website
   3. It could be 2 months from the time you upload an ECG until you see that participant on the EPICARE report.
      - Upload on 3/1/2010
      - DCC submits to EPICARE on 4/1/10
      - EPICARE sends report back on 5/1/10

K. Any questions, problems, concerns about ECG web postings, email the ASSESS_DM alias

Data management procedure – ECG_OTHER

A. ECG_OTHER files will be uploaded by the clinic coordinators to the ASSESS website, and then the DCC will send them on to Wake Forest.
    1. Posting to the ASSESS website is similar to what is described in the above section for ECG_CLINIC
    2. Folders have been added to the ASSESS website under ECGs for EPICARE
        - Post ECGs From Other Sources Here
        - Process remains the same as posting ECGs performed by centers
        - An example has been posted in each center folder for naming each file/description
B. Prepare the ECG printout by affixing a label to it.
    1. This can be completed on a paper copy of the ECG in the same manner used for the ECG_CLINIC files
    2. If the site collects the ECG_OTHER as an electronic file, please complete the header information on the pdf file.
    3. Steps for adding electronic label to the pdf files
        - Open the pdf using Adobe Acrobat Pro (version 10 or 11)
        - Select tools
        - Select Add Text and click on the pdf in the upper right hand corner.
        - Type the header information in the text box (box will expand as you type).
        - You do not need to include the labels for each field (i.e., participant ID, participant initials, etc.). Just type the ID, initials, visit number, visit date and cc_id.
            1. 1-1C-1111
            2. ABC
            3. 3M
            4. 12/01/2014
            5. 12345
C. Review of ECG_OTHER file for PHI is required
    1. To verify that the review of the file was completed, an electronic signature must be added to the file.
    2. Steps for adding the electronic signature
        - Open the pdf using Adobe Acrobat Pro (version 10 or 11)
        - Select 'Fill and Sign'
        - Select 'place signature' and a pop up box will be displayed
        - The default is 'type my name in the box'
        - Type your name in the box and select Accept
        - Place the signature on the pdf file in the bottom right corner if space permits.
        - The signature can be placed on any blank space on the file.
    3. • After completing this signature one time the signature is saved and you can simply click on 'Place signature' and place it on the form. You do not need to keep re-signing.

V. QUALITY CONTROL ISSUES AND PROCEDURES

V.1 Quality grades

The ECG reading center evaluates and ranks the ECG quality. There are 3 grades; 1, 3 and 5. The best grade is 1 and the worst is 5. Grade 3 is given to ECGs that have correctable problems i.e. the ECG problems could be adjusted for on reading them. Grade 5 ECG are given for the ECGs that there have major problems which make it impossible to read them

V.2 Certification/Recertification procedures

- All ECG technicians must go through the certification process before they are allowed to acquire study ECGs.
- Each technician must acquire and successfully submit two (2) good quality ECGs.
- The 2 ECGs should be performed on 2 different volunteers or on 1 volunteer provided that there is at least 30 minutes between each ECG.
- Recertification process (required annually) is the same as the certification process.

V.3. Examples of common ECG quality problems and possible solutions

- EXCESSIVE BASELINE DRIFT (Figure12): This occurs if the participant is moving around or there is tension on the lead wires. Ask the participant to lie still for a few seconds. Drift in excess of 1 mm between baseline points (QRS onset) of any two successive complexes is a sign of significant drift.
- EXCESSIVE MUSCLE NOISE (Figure 13): The participant is either tense due to lack of body support or may be cold. Use a wide bed and blanket to cover the participant.
- BASELINE DRIFT DUE TO TANGLED WIRES (Figure 14): Ensure that the wires are not pulling. Be sure to establish a good electrode connection. Lay a towel across the wires, if necessary. Adjusting the angle of the clip at the electrode often helps. You may need to tape down the chest leads; use only hypoallergenic medical tape to prevent allergic reactions. Use a U loop (not a cross loop) with the electrode wires, i.e., the wire should not cross but remain open like a U; never crossover wires
- LOOSE ELECTRODE CONNECTION (Figure 15): Loose electrode connection may cause a wavy baseline in some ECG leads. Check each electrode to ensure that it is secure. SIXTY HZ NOISE (Figure 16): Periodic 60 HZ noise is sometimes visible in the record. This may be caused by AC interference from a nearby machine. Make a visual check of this before recording the ECG. Unplug any unnecessary surrounding electric equipment *Note:* Jewelry does not cause 60 HZ noise.
- MISSING LEADS AND LEAD REVERSAL (Figures 17-19): To minimize the chances of having lead reversal and missing leads, always make sure that there are no flat lines in the ECG recording and/or mainly positive QRS in aVR lead. Also, always have a second look at the connections before recording.

Figure (12) Excessive baseline drift due to sudden movement of the participant

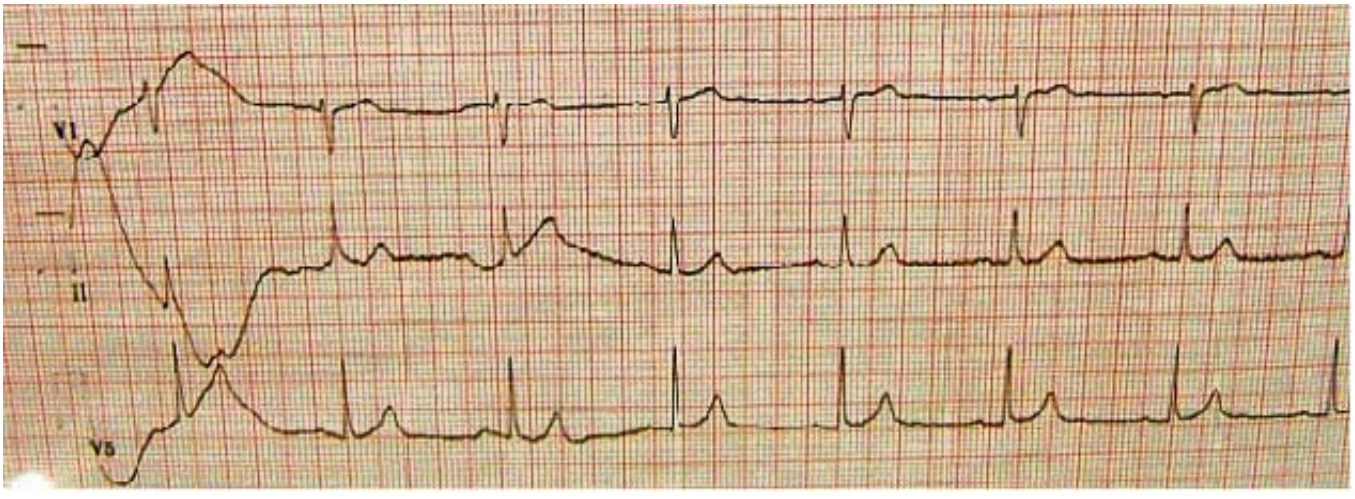


Figure (13) Excessive muscle noise

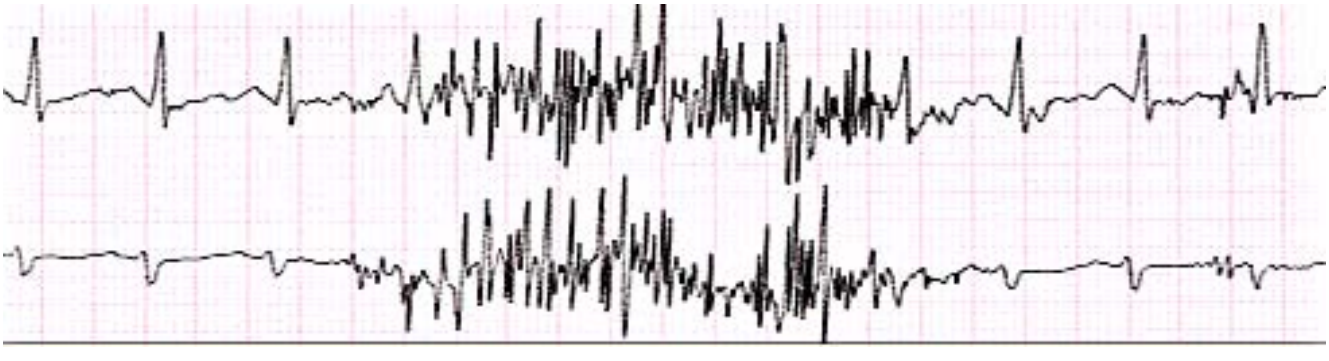


Figure (14) Baseline drift due to tangled wires

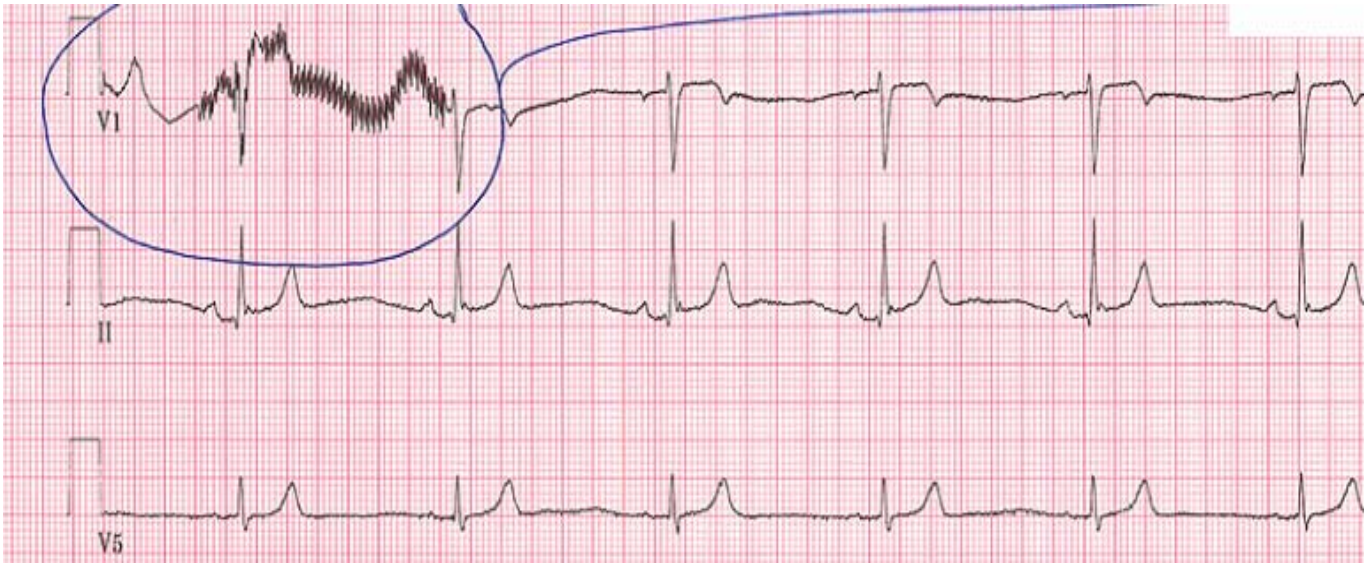


Figure (15) Wavy V1 baseline due to loose electrode

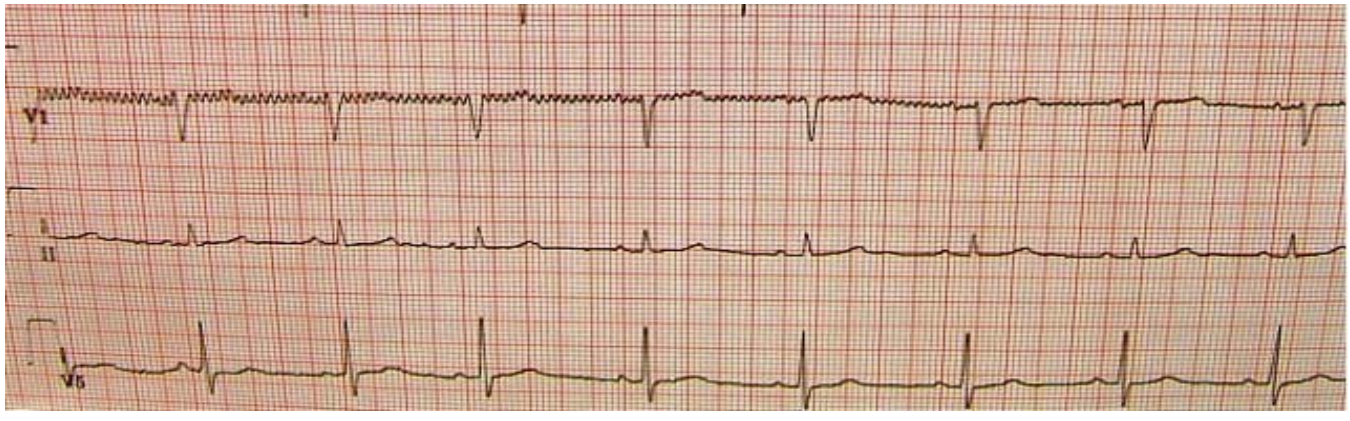


Figure (16) Sixty Hz electrical interference

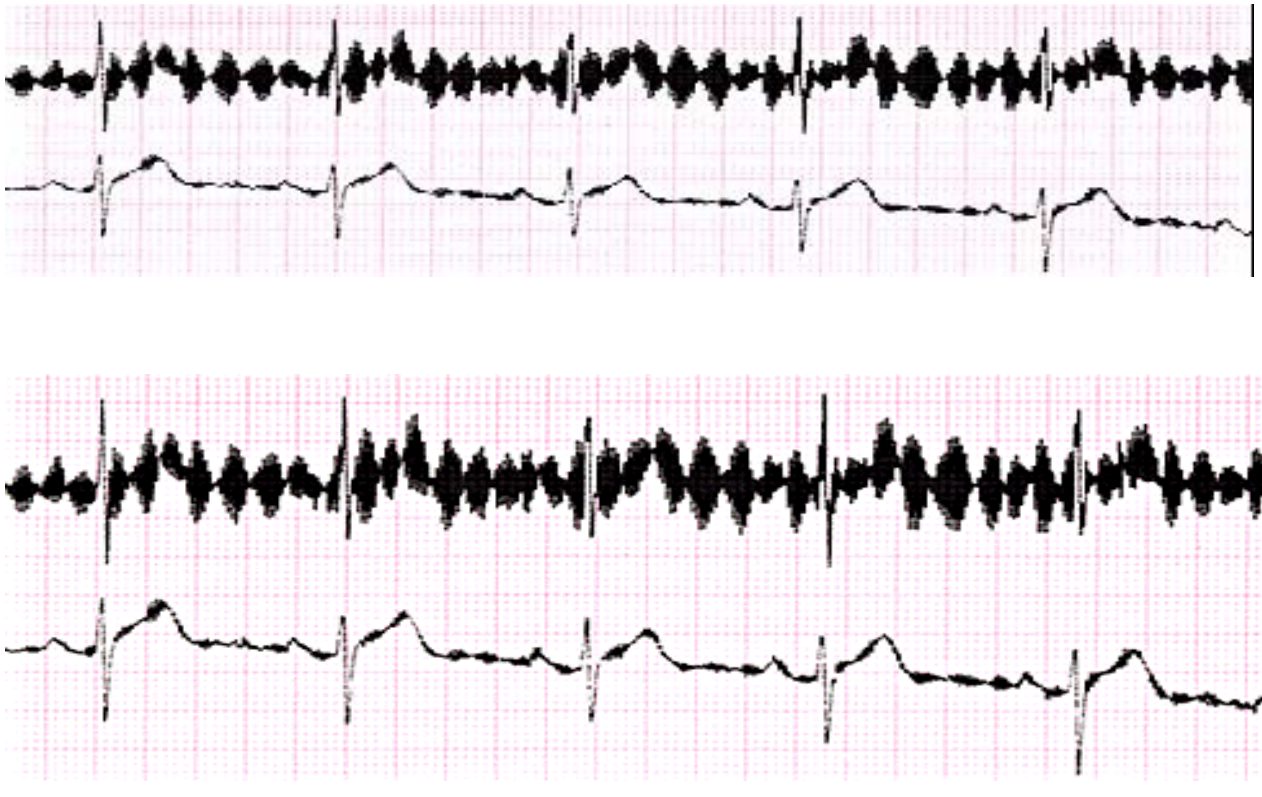


Figure (17) Flat line due to missing V1 lead

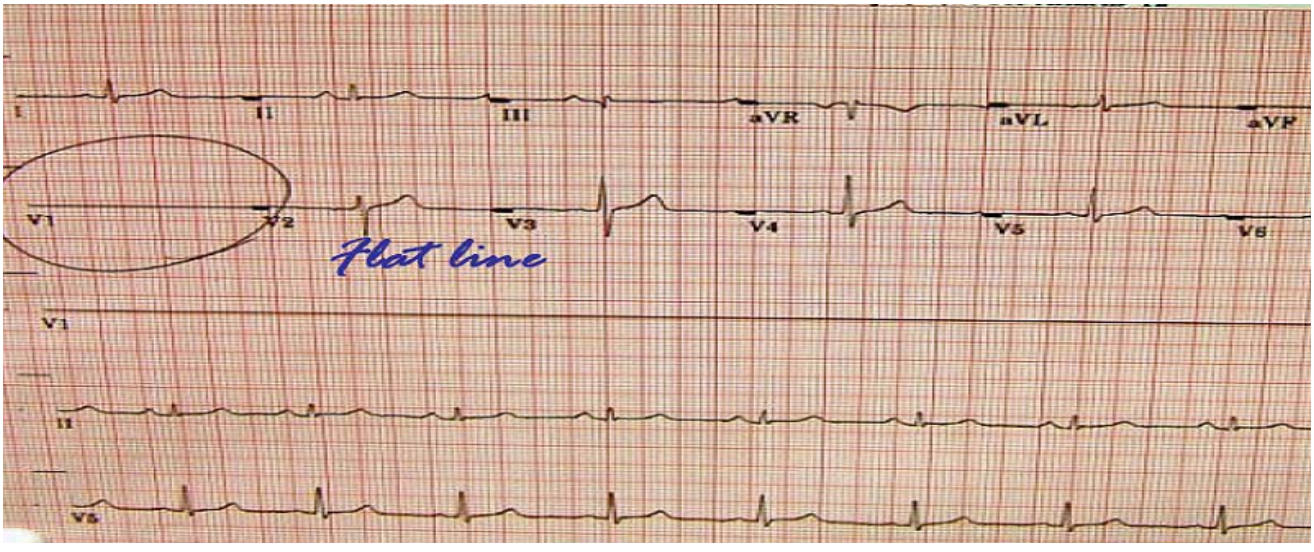
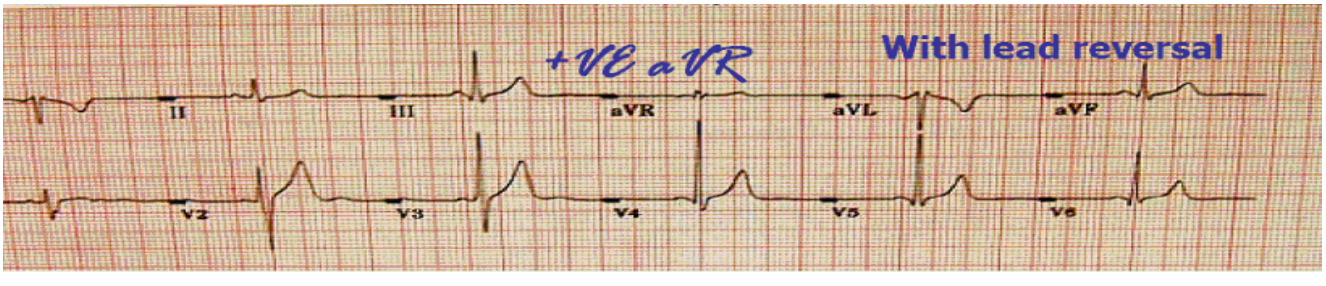


Figure (18) Lead reversal denoted by positive aVR (upper panel) compared to the normal (lower panel)



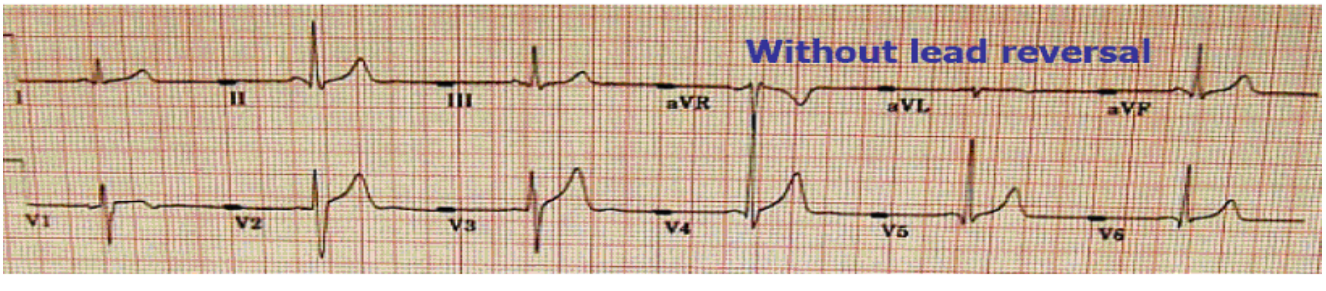


Figure (19) Lead reversal denoted by flat line in one of the limb leads (upper panel) compared to the normal (lower panel)