Protocol

and

Manual of Procedures

November 3, 2008

Sponsored by:

National Institute of Diabetes and Digestive and Kidney Diseases of the National Institute of Health

Careful Urinary Tract Infection Evaluation

The Careful Urinary Tract Infection Evaluation (CUTIE) study is an ancillary study under the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) clinical trial. The CUTIE study protocol is similar to the RIVUR study with the exception that it is an observational study that did not assign treatment arms and the participants did not have vesicoureteral reflux (VUR).

CUTIE based all of its documentation on the RIVUR materials. All aspects of the RIVUR trial that were not applicable to the CUTIE study are crossed out in the manual of operations (MOP) and on the case report forms (CRFs).

Official Protocol and Manual of Procedures

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Chapter 1: Protocol

Protocol No. 2008-2-5793

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National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health (NIH)
Department of Health and Human Services

Building 31. Rm 9A06
31 Center Drive, MSC 2560
Bethesda, MD 20892-2560
USA

Ron Keren, MD, MPH
The Children's Hospital of Philadelphia
3535 Market Street Suite 1524
Philadelphia, PA, 19104
Phone 215-590-0167
email: keren@email.chop.edu

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ABBREVIATIONS AND DEFINITIONS OF TERMS

UTI — Urinary tract infection

Febrile UTI ($_F$UTI) — $_F$UTI requires the presence of (1) fever, (2) pyuria based on urinalysis, and (3) culture-proven infection with a single primary organism[2]. Specifically, the study definition of $_F$UTI requires:

I. Fever[1]
- Documented temperature of at least 100.4 °F or 38°C, measured anywhere on the body either at home or at doctor's office

AND

II. Pyuria on urinalysis
- >10 WBC/mm^3 (uncentrifuged specimen) OR
- >5 WBC/hpf (centrifuged specimen), OR
- Any level of positivity of leukocyte esterase on dipstick

AND

III. Culture proven infection with a single primary organism[2]
- >5 x 10^4 CFU/mL (catheterized or suprapubic aspiration urine specimen) OR
- >10^5 CFU/mL (clean voided specimen)

Symptomatic Non-febrile UTI ($_S$UTI) — $_S$UTI requires the presence of (1) urinary tract symptoms, (2) pyuria on urinalysis, and (3) culture-proven infection with a single primary organism[2]. Specifically, the study definition of $_S$UTI requires:

I. Symptoms[1]
- Suprapubic, abdominal, or flank pain or tenderness, or urinary urgency, frequency, or hesitancy, or dysuria, or foul smelling urine, or in infants ≤ 4 months old, failure to thrive, dehydration, or hypothermia

AND

II. Pyuria on urinalysis
- >10 WBC/mm^3 (uncentrifuged specimen) OR
- >5 WBC/hpf (centrifuged specimen), OR
- > Any level of positivity of leukocyte esterase on dipstick

AND

III. Culture proven infection with a single primary organism[2]
- >5 x 10^4 CFU/mL (catheterized or suprapubic aspiration urine specimen) OR

[1] Must occur within ± 24 hours of initiating work-up for UTI.

[2] Index UTI culture may also include 1 additional secondary organism with colony count <10,000 CFU/mL (<10X10^3)

	• $>10^5$ CFU/mL (clean voided specimen)
Febrile or Symptomatic UTI ($_{F/S}$UTI)	As defined above in Febrile UTI ($_F$UTI) and Symptomatic Non-febrile UTI ($_S$UTI)
Index UTI	UTI that leads to VCUG and patient recruitment for the study. The index UTI may be either: (1) The participant's first febrile or symptomatic UTI OR (2) The participant's second UTI which is either febrile or symptomatic, and where the first UTI did ***NOT*** result in either: • the patient being placed on antimicrobial prophylaxis, **or** • the diagnosis of VUR Date of diagnosis for the index UTI is the date that the urine specimen that resulted in a positive culture was collected.
Recurrence of UTI	Infection more than 14 days after end of appropriate treatment of a UTI, or following a negative urine culture, or infection with a new organism.
Persistent UTI	Evidence of infection within 14 days after end of treatment of a UTI, in the absence of an intermediate negative urine culture (indicating that the treated UTI was never resolved).
Vesicoureteral Reflux (VUR)	VUR is defined as the retrograde flow of urine from the bladder up the ureter. It may or may not reach the level of the renal pelvis producing dilation of the upper urinary tract (see figure 5, section 3.1.2b)
VCUG	Voiding Cystourethrogram
Renal scarring (determined by DMSA)	Renal scarring will be defined as decreased uptake of tracer associated with loss of contours or cortical thinning. In order to quantify the extent of renal scarring, each kidney will be divided into 12 segments and a five level grading system will be applied. Severe scarring will be defined as the presence of grades 3 or 4 scarring on at least 1 kidney (see figure 7, section 4.1).
Dysfunctional voiding	A dysfunctional voiding symptoms score (DVSS) of more than 6 in female and more than 9 in male children ≥3 years of age using a standardized scale [1].
Chronic constipation in the toilet trained child, as defined by the Paris Consensus on Childhood Constipation Terminology (PACCT) Group [2]	The occurrence of 2 or more of the following during the last 8 days in the toilet-trained child • Frequency of bowel movement < 3 / week • More than one episode of fecal incontinence / week • Large stools in the rectum or palpable on abdominal examination • Passing of large stools that may obstruct the toilet • Display of retentive posturing and withholding behaviors • Painful defecation
Treatment failure:	Treatment failure is defined by: I. In any participant:

- Occurrence of 2 recurrent $_{F}$UTIs or a total of 4 recurrent $_{F/S}$UTIs within the study period, OR
- Interim 12-month scan shows new or worsening scarring at a site different from the index APN or worsening scarring evidenced by extension of a preexistent scar seen on the baseline DMSA scan (note, the interim scan may serve as the outcome DMSA scan in these participants).

OR

II. In children with baseline scarring grade 3 or higher:

- Children whose initial DMSA scan shows grade 3 or higher scarring in either kidney will have a repeat DMSA performed at the time of any recurrent $_{F}$UTI; if additional renal segment involvement is observed (APN or scar) compared with the baseline scan, then the child will be categorized as treatment failure and have an outcome DMSA scan at approximately 4 months following the $_{F}$UTI. If no additional renal segment involvement is observed, the child will continue in the study as assigned.

Appropriately treated UTI

Treatment for UTI will be considered appropriate if antibiotic therapy continues for a minimum of 7 days and:

I. There is documented sensitivity of the organism to the antibiotic used for treatment OR
II. There is a documented test of cure (negative urine culture) 1-14 days after completion of therapy.

Society of Fetal Urology (SFU) grading of hydronephrosis

Grade 0 - No hydronephrosis, intact central renal complex.
Grade 1 - Only renal pelvis visualized. Dilated pelvis on ultrasound.
Grade 2 - Moderately dilated renal pelvis and few calyces seen.
Grade 3 - Hydronephrosis with nearly all calyces seen. Large renal pelvis and good parenchyma.
Grade 4 - Hydronephrosis with nearly all calyces seen and parenchymal atrophy or thinning.

PROTOCOL SYNOPSIS

STUDY TITLE	
SPONSOR	National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) National Institutes of Health (NIH)
CLINICAL PHASE	N/A
STUDY RATIONALE	Urinary tract infection (UTI) is the most common serious bacterial infection in young children. Estimates of cumulative incidence of UTI in children younger than 6 years of age (3-7% in girls, 1-2% in boys)[3-5] suggest that 70,000 to 180,000 of the annual US birth cohort will have a UTI by age six. Approximately two-thirds of young children with febrile UTI will have acute pyelonephritis (APN), which involves infection and inflammation of the kidneys and ureters,[6-9] and between 15 and 52 per cent of children with APN will develop subsequent renal scarring.[6, 7, 10-12] The current standard of care for young children who present with UTI is to perform a voiding cystourethrogram (VCUG) to evaluate for the presence and degree of vesicoureteral reflux (VUR),[13] a condition present in approximately 30-40% of children with UTI,[14] in which urine flows retrograde during micturition from the bladder towards the kidneys. Until recently, it was widely accepted that VUR increased the risk of renal scarring from UTI[15-17], and so it was recommended that children with UTI and VUR have surgical correction of their VUR and/or receive daily antimicrobial prophylaxis to prevent UTI until the VUR resolves.[13, 18] In recent years, our understanding of the relationship of UTI, VUR, and renal scarring, and current strategies for managing children with UTI have been challenged.[19-22] It is now clear that renal scarring can occur in children who do not have VUR, and that most children who have even high grade VUR do not develop renal scarring.[7, 10, 11, 23-25] Analyses of dialysis and transplant registries suggest that the diagnosis and treatment of children with VUR that started in the 1960's have not been associated with a reduction in the incidence of end stage renal disease attributable to reflux nephropathy.[26, 27] Furthermore, older studies comparing the effectiveness of combined surgical correction and prophylactic antibiotics to prophylactic antibiotics alone, and more recent studies comparing prophylactic antibiotics to placebo, have shown no difference in rates of renal scarring,[21, 28-33] raising doubts about the significance of VUR in the progression to renal scarring, and the efficacy of either surgery or prophylactic antibiotics compared with prompt evaluation of urinary symptoms and early treatment of confirmed UTI.[6, 21] In the fall of 2005 the NIDDK began funding a 5-year multicenter randomized placebo-controlled trial to evaluate the effectiveness and harms of prophylactic antimicrobials for the prevention of recurrent UTIs and renal scarring in children with VUR diagnosed after a first or second UTI (**RIVUR**—Randomized Intervention for Vesicoureteral Reflux; U01-DK074064). Because the goal of RIVUR is to evaluate the current paradigm of UTI management, which maintains that VUR is the main factor to be considered in determining which patients with UTI require antimicrobial prophylaxis, the study will enroll only patients who have VUR. However, the RIVUR protocol offers a unique opportunity to study the risks of renal scarring after UTI in children who do not have VUR. Three of the clinical trial centers participating in RIVUR will be recruiting patients at the time of UTI diagnosis (as opposed to after a diagnosis of VUR) and will be screening them for presence of VUR. By enrolling the children who do not have VUR into an ancillary study and following them for recurrence of UTI and development of renal scarring, we will be able to understand more completely the factors that place a child at risk for developing renal scarring, regardless of whether he/she has VUR.

Understanding which children are at the greatest risk of renal scarring after a UTI may allow us to provide more targeted therapies and interventions. Furthermore, by banking urine and blood from the children in both RIVUR and this proposed ancillary study, we create future opportunities to examine the genetic determinants of renal scarring in all children with UTI.

STUDY OBJECTIVE(S)

Specific Aims:

1) **To compare the proportion of children who develop renal scarring 2 years following a first or second episode of UTI among children in the proposed ancillary study who do not have VUR and children in the RIVUR study who do have VUR and are receiving placebo.**
Hypothesis: The proportion of children who develop renal scarring among children in the ancillary study who do not have VUR and children in the RIVUR study who do have VUR and are receiving placebo will be equivalent (<10% absolute risk difference).

2) **To develop a prediction rule that accurately identifies children at high risk of developing renal scarring as well as children with virtually no risk of developing renal scarring following a first or second episode of UTI.**
Hypothesis: A prediction rule incorporating clinical and demographic factors associated with renal scarring will predict with >98% sensitivity and >50% specificity which children will develop renal scarring following a first or second episode of UTI. A prediction rule with these test properties would identify nearly all children who develop renal scarring while accurately assessing as low risk at least 50% of children who do not develop renal scarring.

Secondary Aims:

1) **To compare the proportion of children who experience a recurrent UTI following the index UTI episode among children in the proposed ancillary study who do not have VUR and children in the RIVUR study who have VUR and are receiving placebo.**
Hypothesis: The proportion of children who experience a recurrent UTI among children in the ancillary study who do not have VUR and children in the RIVUR study who do have VUR and are receiving placebo will be equivalent (<10% absolute risk difference).

2) **To develop a prediction rule that accurately identifies children at high risk of experiencing a recurrent UTI as well as children with virtually no risk for recurrence following a first or second episode of UTI.**
Hypothesis: A prediction rule incorporating clinical and demographic factors associated with renal scarring will predict with >98% sensitivity and >50% specificity which children will have a recurrent UTI. A prediction rule with these test properties would identify nearly all children who go on to experience UTI recurrence while accurately assessing as low risk at least 50% of children who do not experience UTI recurrence.

TEST ARTICLE(S) *(if applicable)* N/A

STUDY DESIGN	We propose to conduct a multi-center prospective cohort study comparing rates of renal scarring and recurrent UTI after a first or second UTI in 2 groups of children—one group of children who do not have VUR and one group of children who do have VUR and are treated as part of the RIVUR protocol with placebo. All participants will be enrolled over an 18-24 month period and followed for 2 years post-enrollment.
SUBJECT POPULATION **Main criteria for inclusion and exclusion:**	**Inclusion Criteria** 1) Age at enrollment 2-72 months. Note that children as young as 1 month may be screened for study. 2) Diagnosed first or second $_{F/S}$UTI within 112 days (16 weeks) prior to enrollment 3) Appropriately treated first or second $_{F/S}$UTI 4) Parental/guardian permission (informed consent) and if appropriate, child assent. **Exclusion Criteria** 1) For children less than 6 months of age at randomization, gestational age <34 wks 2) UTI diagnosis more than 112 days (16 weeks) prior to enrollment 3) Index UTI not appropriately treated 4) VUR (Grades I-V) diagnosis by VCUG 5) Co-morbid urologic anomalies 6) History of other renal injury/disease 7) Congenital or acquired immunodeficiency 8) Complex cardiac disease 9) Any known syndromes associated with VUR or bladder dysfunction 10) Unable to complete the study protocol 11) Unlikely to complete follow-up
NUMBER OF SUBJECTS	
Overall and at CHOP	360 overall; 120 at CHOP
Number of Study Sites	3
STUDY DURATION	
Duration subject participation	2 years
Expected Study Duration	4 years
STUDY PHASES	
Screening	2 years
Observation	2 years
EFFICACY EVALUATIONS	N/A
PHARMACOKINETIC EVALUATIONS *(if applicable)*	N/A
SAFETY EVALUATIONS	All subjects entered into the study at Visit 1 will be included in the safety analysis. The frequencies of AEs by type, body system, severity will be summarized. SAEs (if any) will be described in detail. This is an observational study and so we will report only AEs and SAEs directly related to the study and not to underlying illness.
STATISTICAL AND ANALYTIC PLAN	In order to test whether the proportion of children who have renal scarring on DMSA scan is equivalent among the ancillary study patients who did not have VUR and the placebo-treated RIVUR study who did have VUR, we will

	calculate the difference in proportions and test whether the difference in proportions is less than 10% or not using a one-sided 0.05 significance level. We will therefore test the null hypothesis that the VUR group and non-VUR group are not equivalent and that the difference in the proportions of renal scarring between the groups is 10% or farther from zero in the same direction. Multivariable modeling techniques will be used to develop prediction models for the development of renal scarring.[34-36] Clinical judgment and strength of predictive variables in previous studies will force some variables to be included in the models regardless of their level of statistical significance (e.g., VUR grade, age, sex). Potential interaction variables to be considered in the models will be chosen based on the clinical judgment of the investigators and evidence from the literature, if both variables are candidates for inclusion in the model based on the first step The analytic approach of (1) testing for equivalence of proportion of recurrent UTIs between patients who had VUR and were treated with placebo after their first or second UTI (RIVUR patients) and patients who did not have VUR after their first or second UTI (recruited as patients to this study) and (2) building a predictive model will be identical to the approach described above for the renal scarring outcome.
DATA AND SAFETY MONITORING PLAN	Because this is an observational study, we will not establish an independent Data and Safety Monitoring Board (DSMB) for this study. The site PIs will be charged with approving and/or making recommendations to the final draft of the protocol, as well as monitoring recruitment and retention and reviewing data for safety. Table 12 details the frequency and types of reports as part of this plan.

TABLE 1: SCHEDULE OF STUDY OBSERVATIONS AND PROCEDURES

Study Month Type of Contact	-2 to 0 (Visit) Screening	0 (Visit) Randomization/ Baseline	6 month (Visit) Follow-up	12 month (Visit) Follow-up	18 month (Visit) Follow-up	24 month (Visit) Follow-up		Every 2 months (Phone) Follow-up
Ultrasound	X*							
Contrast VCUG	X*							
Informed Consent	X							
DMSA		X**		†		X***		
Detailed Medical History		X						
Interim History		X	X	X	X	X		X
Physical Examination		X	X	X	X	X		
Questionnaires								
Dysf Void Symp Score and PACCT (age ≥3)		X		X		X		
Parent diary		X	X	X	X	X		X
QOL assessment		X		X		X		
Urine tests								
Urinalysis		X				X		
Culture		X††				X††		
Microalbumin/ Creatinine		X				X		
Urine for central Repository		X				X		
Blood tests								
Creatinine, lutes		X				X		
Cystatin C		X				X		
Blood for central Repository		X				X		
Telephone Follow-up								X

*Screening ultrasound and VCUG may occur any time within 16 weeks following the index UTI as standard of care procedure.

**Screening DMSA may occur within 2 weeks following randomization and no more than 16 weeks after the index UTI.

***24 month DMSA scan may not occur if a study outcome scan has already been obtained.

†A DMSA scan will be performed at 1 year if there is an interim febrile UTI.

†† If urinalysis positive, culture is obtained

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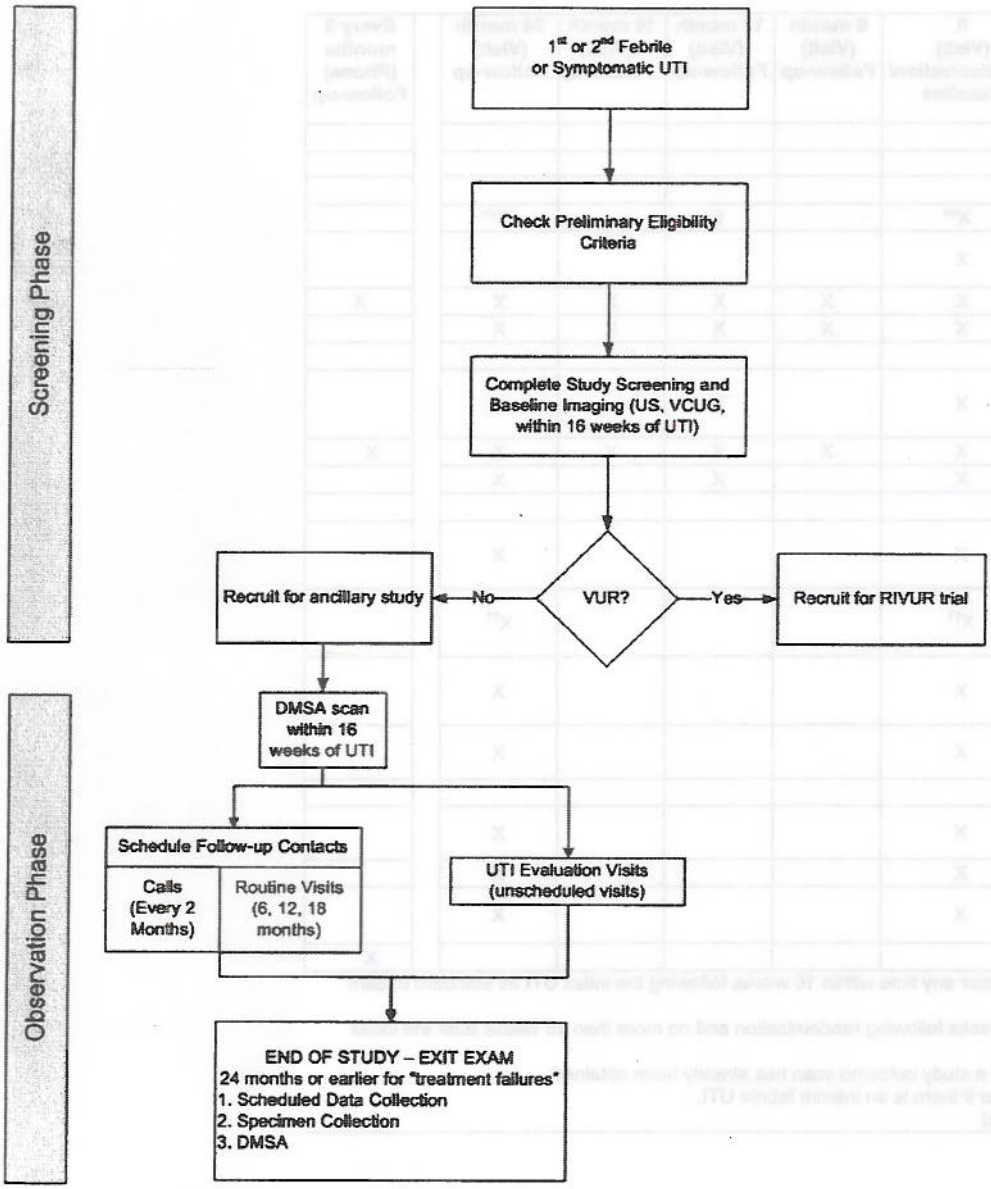
FIGURE 1: FLOW DIAGRAM FOR PROPOSED ANCILLARY STUDY



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Background and Significance

1.1.1 Epidemiology of UTI, Renal Scarring, and VUR

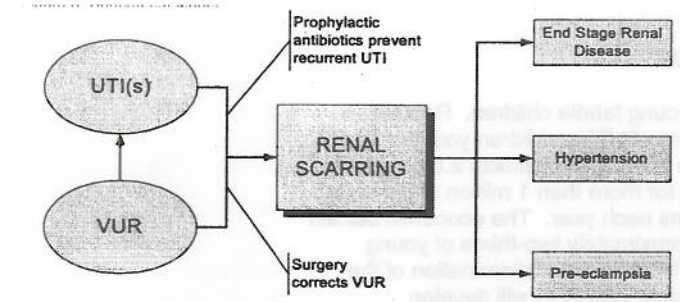
UTI is the most common serious bacterial infection in young febrile children. Population based studies suggest that the cumulative incidence rate of UTI in children younger than 6 years of age is between 3% to 7% for girls and 1-2% in boys.[3-5] UTI affects 2.6% to 3.4% of children in the United States annually, and accounts for more than 1 million office visits, 94,000 hospital outpatient visits and ~40,000 admissions each year. The economic burden for UTI hospitalizations alone totals $180 million.[37] Approximately two-thirds of young children with febrile UTI will have APN, which involves infection and inflammation of the kidneys and ureters.[6-9] Between 15% and 52% of children with APN will develop subsequent renal scarring.[6, 7, 10-12] With significant scarring, renal insufficiency or renal failure necessitating hemodialysis may occur. Additionally, hypertension has been associated with renal scarring in 17% to 30% of children.[38-41]

The current standard of care for young children diagnosed with a UTI is to perform an imaging procedure to evaluate for the presence of vesicoureteral reflux (VUR),[13] a condition in which urine flows retrograde during micturition from the bladder towards the kidneys. Children with UTI are screened for VUR because it is thought to be the strongest predictor of renal scarring. The prevalence of VUR reported in larger epidemiological studies is in the 30% to 40% range.[14] VUR prevalence decreases with age[14] and is higher in males and children with a family history of uropathology.[42, 43] Most observed VUR is low grade. Meta-analyses of VUR prevalence show that about half of children with VUR have grades I to II (out of V).[14]

1.1.2 Relationship of UTI and VUR to Renal Scarring

VUR is thought to increase the risk of UTI by increasing post-void residual and allowing less virulent strains of bacteria to ascend into the upper tract and infect the kidney. VUR is considered important in the evaluation and management of children with UTI because of the observed relationship between degree of VUR and subsequent renal scarring. In some studies, patients with high-grade VUR have been four to six times more likely to have scarring than those with low-grade VUR and eight to ten times as likely as those with no VUR.[15-17] Based on these associations, a conceptual model has evolved postulating that the combination of recurrent UTI and VUR leads to renal scarring (Figure 2). As a result, management strategies have focused on surgical correction of VUR and/or prevention of UTI with prophylactic antibiotics.[13]

Figure 2: Conceptual Model of Renal Scarring



Recently, however, these management strategies and the conceptual model from which they derive have been called into question.[19-22] Critics point out that the idea that VUR potentiates renal scarring from UTI originated in experiments in piglets[44] and is not based on strong empiric evidence from studies in humans. The International Reflux Study and other randomized controlled trials that compared combined surgery and prophylactic antibiotics to prophylactic antibiotics alone also raised doubts about this model. If VUR contributed significantly to the development of renal scarring from UTI, then in those trials surgical correction should have decreased renal scarring compared with antibiotic prophylaxis alone. However these trials showed no incremental difference in rates of renal scarring with surgical correction and prophylactic antibiotics compared with prophylactic antibiotics alone.[29-33] Because none of these studies included a placebo or "observation only" arm, the question has also been raised as to whether surgery **or** prophylactic antibiotics has **any** effect on renal scarring for children with UTI and VUR. Interestingly, analyses of dialysis and transplant registries show that the diagnosis and treatment of children with VUR that started in the 1960's has not been associated with a reduction in the incidence of end stage renal disease attributable to reflux nephropathy.[19, 26, 27] Finally, a recent placebo-controlled trial of prophylactic antibiotics showed that after 1 year of follow-up monitoring, prophylactic antibiotics did not decrease the incidence of UTI, pyelonephritis, or renal scarring after acute pyelonephritis.[25]

Most importantly, however, it is now clear that although severity of VUR is associated with renal scarring, **VUR is neither necessary nor sufficient for the development of renal scarring in children with UTIs.** That is, renal scarring has been documented in children with no VUR, and most children with even high grade VUR do not develop renal scarring. Multiple individual studies as well as a meta-analysis on this topic have demonstrated this dissociation between VUR and renal scarring.[7, 10, 11, 23, 24] Rushton and Majd were among the first to make this observation, first in the relationship between VUR and acute pyelonephritis (the precursor to renal scarring), and later with actual renal scarring. In a prospective clinical study of 94 consecutive children with febrile UTIs,[45] they found that only 37% of acute DMSA scan positive patients had VUR. When reflux was present, 79% of the patients had DMSA scan findings of acute pyelonephritis, including all patients with Grade III or higher VUR. Similarly, 60% of patents without demonstrable reflux had findings of acute pyelonephritis on DMSA renal scans. Subsequent prospective studies showed that new renal scarring also occurred equally as often in kidneys without VUR (43%) as in those with vesicoureteral reflux (40%).[7] Similar findings have been observed by others.[10, 16, 46, 47] In a meta-analysis of studies comparing the results of VCUG to DMSA, the pooled

likelihood ratio positive for presence of VUR on VCUG in the prediction of renal parenchymal disease on DMSA was only 1.96 (95% CI, 1.51 to 2.54).

Instead of VUR, the common denominator in all cases of post-infectious renal scarring appears to be inflammatory response to acute infection of the renal parenchyma. Using serial DMSA renal scans, investigators have observed that acute DMSA renal scan defects can persist as renal scarring in infected kidneys and that the sites of new renal scarring correspond exactly to those sites of acute pyelonephritis seen on the initial DMSA renal scans.[6, 7, 10-12] Contralateral normal kidneys and initially uninvolved areas of abnormal kidneys almost always remain normal on follow-up DMSA renal scans. These observations provide convincing clinical evidence that renal parenchymal infection, rather than VUR, is the prerequisite for acquired (postnatal) renal scarring. Once bacteria have invaded the renal parenchyma, the inflammatory response appears similar and the propensity for renal scarring is equally as great whether or not VUR is present.

Despite these findings, the importance of VUR (particularly Grades III or higher) as a risk factor for renal scarring should not be completely discounted. Clearly, children with moderate and severe reflux are much more likely to develop acute pyelonephritic damage than children with mild or no reflux.[10, 45] Furthermore, although 62 per cent of the kidneys with post-pyelonephritic renal scarring in one study were drained by nonrefluxing ureters, renal scarring was still significantly more common in those kidneys with Grade III or higher VUR compared with kidneys with mild or no reflux.[10] Thus, the increased propensity for scarring in children with higher grades of VUR is attributable in part to the increased risk of these kidneys for acute inflammatory damage at the time of the initial infection.[10, 45, 48] Indeed, in one study that attempted to quantitate the area of acute pyelonephritic parenchymal damage, the presence of grade $\geq$ 3 reflux was associated with a significantly greater frequency of kidneys demonstrating large defects (defined as >10 per cent of the kidney demonstrating DMSA uptake <2 SD of the control kidney) when compared to kidneys with no VUR ($p < 0.02$). Thus, when present, moderate or severe reflux (grade $\geq$3) remains the most significant host risk factor for acute pyelonephritis and renal scarring.

1.1.3 Other Predictors of Renal Scarring

It is not known why some children with APN develop renal scars while others heal without consequence, although multiple host and bacterial factors have been implicated. Given that the mere presence of VUR does not accurately discriminate between children at low and high risk of developing renal scarring after an episode of UTI, investigators have attempted to identify other factors associated with renal scarring. These include host factors (mechanical, hydrodynamic, anti-adherence, receptor-dependent and immunologic) that affect an individual's susceptibility to UTI, as well as bacterial virulence factors involved in adherence, colonization, invasion, and resistance to host defenses. Two older studies analyzed the association of various clinical and bacteriologic parameters with the development of new renal scarring.[7, 10] In both studies, children who developed new renal scars were actually older at the time of acute pyelonephritis although the difference was statistically significant in only one.[10] An elevated white blood count at the time of the initial infection was not associated with renal scarring. When comparing children with and without new scarring, no significant differences were noted in race, gender, duration of fever, maximum temperature, or acute inflammatory markers (CRP, ESR) at the time of the acute pyelonephritic episode. E.coli was cultured from the urine of 88% to 95% of the children in both studies. Interestingly, new renal scarring occurred in 33% to 41% of children infected with E.coli compared with 100% of children in both studies who were infected with other

bacteria. In one study no significant association was found between bacterial virulence factors (hemolysin, colicin, P-fimbriae) and renal scarring, although colicin production was found almost twice as often in the bacteria isolated from children with new renal scarring.[7] In a more recent report of 157 children evaluated with a DMSA renal scan one year following their first-time symptomatic UTI, children with high levels of CRP, high fever, and dilating VUR were ten times more likely to have scarring than children with normal or slightly elevated CRP levels, no or mild fever, and no VUR.[49]

Dysfunctional voiding refers to overactivity of the pelvic floor muscles during the voiding phase of the micturition cycle. It is relatively common in the pediatric population (prevalence approximately 15 percent)[50], and is often underdiagnosed and undertreated by primary care physicians.[51] Approximately 40 percent of toilet-trained children with their first UTI[52-54] and 80 percent of children with recurrent UTI[55] report symptoms of dysfunctional voiding. In a study of 141 girls older than 3 years of age with recurrent (three or more) UTIs, 108 (77%) had dysfunctional voiding symptoms.[55] Dysfunctional voiding also is a risk factor for VUR persistence[56-58] and renal scarring.[52, 53] Dysfunctional voiding is best assessed through urodynamic studies but these are invasive and uncomfortable for most children. Non-invasive studies to identify contracted pelvic floor muscles with voiding include uroflowmetry, surface electrode EMG, and measurement of ultrasound post-void residual. The Dysfunctional Voiding Scoring System, developed and validated by Farhat et al.,[1, 59] is a noninvasive instrument for identifying symptoms of voiding dysfunction and monitoring compliance with therapy.[60]

More recently, a greater emphasis has been placed on searching for genetic determinants of renal scarring following UTI. Candidate genes involved in innate immunity and tissue repair mechanisms, such as toll-like receptor, type -2 and -4, TNF-α, TGF-β, and components of the renin-angiotensin system have been variably implicated in renal scarring by single institutions and often on poorly defined patient populations with heterogeneous pediatric urological diagnoses. Two well controlled studies found strong associations between polymorphisms of TNF-α (AA (-308)) and TGF-β (CC Lue(10)–>Pro (codon 10)) with reflux nephropathy, but no functional significance has yet been identified.[61, 62]

Prior studies designed to identify risk factors for renal scarring have had several significant limitations to their internal validity and generalizability. First, most studies had very small sample sizes (33-157; mean=89), significantly limiting their power to detect associations between risk factors and scarring. For example, assuming a study enrolled 100 subjects, one-third of whom had the risk factor of interest, and the rate of scarring in the group without the risk factor was 10%, the study would have only enough power to detect an odds ratio (OR) of 5.1 for that risk factor (assuming power=80% and alpha=0.05). Starting out with fewer subjects (as was the case with 2 of the 3 prior studies) and a lower rate of scarring in the unexposed group (subjects who do not have the risk factor) would increase the smallest detectable OR even further. In other words, only risk factors that were very strongly associated with renal scarring would have been detectable in these studies. The second limitation of prior studies is that they generally sought to determine the predictive value of one, or at most two, risk factors for renal scarring and did not employ multivariable models to increase the explanatory power of several factors associated with that outcome. By increasing the sample size and including factors that are even modestly associated with renal scarring, we expect to derive predictive models in the proposed study that have greater explanatory power. Prior studies have also included highly selected populations, for example exclusively hospitalized children or children with a history of multiple previous UTIs. By enrolling an inception cohort of children with their first or second documented UTI

and recruiting from primary care as well as sub-specialty and inpatient settings, we expect that our results will be more reflective of the overall population of children with UTIs and therefore more generalizable. Finally, but most importantly, prior studies have included children treated with prophylactic antimicrobials, which may have affected renal scarring rates. By combining data from placebo treated children in RIVUR who have VUR and untreated children in the proposed ancillary study who do not have VUR, we will have the unique, and perhaps only, opportunity to understand the risk factors for renal scarring after UTI in the absence of antimicrobial prophylaxis.

1.1.4 Background to Imaging Studies

A number of imaging techniques have been utilized to evaluate the child with a UTI. Radiographic VCUG remains the gold standard for identification and evaluation of VUR. Renal ultrasound; identifies hydronephrosis but is insensitive to identifying renal scarring. A number of procedures and tests have been used to try to localize the site of UTI to the upper (acute pyelonephritis, or APN) or lower (cystitis) urinary tract. An acute phase response consisting of elevated peripheral white blood cell (WBC) count, erythrocyte sedimentation rate and C-reactive protein were used in several studies to indicate infection of the upper urinary tract. However, as noted in a review article by Rushton and in editorials by Andrich and Majd, Conway, and Hellerstein, children who have a first UTI accompanied by fever and toxicity cannot be diagnosed reliably as having APN based on clinical signs and symptoms or laboratory parameters alone [63, 64]. Currently DMSA scintigraphy has emerged as the imaging agent of choice for the detection and evaluation of APN and renal cortical scarring in children. Using strict histopathologic criteria in the refluxing infected piglet model, DMSA renal scans have been found to be highly sensitive and specific for the detection and localization of APN [64, 65]. The DMSA scan also has shown higher sensitivity and specificity than intravenous pyelography (IVP) in documenting renal scars in several clinical studies, and has shown good correlation with histopathology in animal data [66-70]. Consequently, DMSA renal scintigraphy provides a unique opportunity to study the progression of renal damage and functional loss from the initial insult of APN to the subsequent development of irreversible renal scarring [7]. Accordingly, DMSA renal scanning is considered to be the "gold standard" for identifying renal parenchymal changes, and is recommended as the primary study for diagnosis of APN and renal scarring [63, 64, 71, 72]. As such DMSA renal scans will be used in the study as the outcome measurement for the detection and semi-quantification of both preexistent and newly acquired renal parenchymal damage associated with UTIs in children with Grades I-IV VUR.

1.1.5 Significance of Proposed Research

The proposed study will allow us to determine the contribution of VUR, as well as other risk factors, to the development of renal scarring in an inception cohort of children who present with their first or second UTI. If, in addressing **Aim 1**, we find that the children in the ancillary study who do not have VUR have the same rate of renal scarring as the placebo-treated children in the RIVUR study who have VUR, then our results would confirm that the presence of VUR on VCUG is inadequate for identifying children at risk of developing renal scarring and targeting children for intervention (e.g. prophylactic antibiotics). If, as in prior studies, it is shown that the presence of DMSA uptake defects on renal scintigraphy performed shortly after the UTI are more predictive of which children will develop renal scarring than the presence of VUR on VCUG, these results would argue for a paradigm shift in the diagnostic evaluation of children with a first or second episode of UTI, with

DMSA scan supplanting (or at the very least augmenting) VCUG as an important first study. If neither presence of VUR nor DMSA uptake defects alone accurately predict which children will develop renal scarring, then a prediction model developed (for **Aim 2)** on a large group of children with first or second UTI may help to identify clinical and demographic factors that, in combination with VCUG and DMSA findings, identify a group of children at high (and low) risk of developing renal scarring. Such a rule could be used to identify high-risk candidates for future interventional studies to prevent renal scarring. Finally, if clinical, radiographic, and demographic factors do not stratify patients in terms of their risk of renal scar development after a first or second UTI with sufficient accuracy, then the collection of blood and urine microbiological specimens will allow for future studies to be performed to evaluate more specific host genetic and microbiological factors as potential predictors of renal scarring.

The significance of our results will also depend on the results of the parent RIVUR study. If the renal scarring rate in children who do not have VUR approaches or exceeds the renal scarring rate in placebo treated RIVUR subjects who do have VUR, AND prophylaxis is found to be effective in the RIVUR trial, then the benefit of prophylaxis in children with no VUR will need to be evaluated in a future study. If prophylaxis is not found to be effective for children with VUR in the RIVUR trial, then the proposed ancillary study may identify other factors associated with renal scarring which can be used to target children with high risk of renal scarring in future studies of interventions (such as prophylactic antibiotics) to prevent renal scarring.

If the renal scarring rate in children who do not have VUR is far less than the renal scarring rate in placebo treated RIVUR subjects who do have VUR, AND prophylaxis is found to be effective, then we will have confirmed the effectiveness of the current paradigm of care, in which all children with first or second UTI have a VCUG and only those with VUR receive prophylactic antibiotics. If prophylaxis is not found to be effective, then we will have learned that neither prophylaxis nor VCUGs are useful in children with first or second UTI. Thus, regardless of the results of the RIVUR study, the proposed ancillary study has the potential to yield important results with significant implications for management of UTIs and/or future studies.

1.1.6 Importance of the Knowledge to be Gained

This study will determine risk factors for renal scarring and recurrent UTI in both children who do and not have VUR. The results of this trial will have profound implications on the recommended radiological evaluation and treatment of children with UTI. The risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

1.2 Preliminary Studies

1.2.1 Overview

The members of this multi-disciplinary investigative team have contributed significantly to the literature concerning the epidemiology, diagnosis, evaluation, and management of children with UTI and VUR. Preliminary data from our electronic databases demonstrate that the 3 clinical trial centers that will be part of this ancillary study will be capable of recruiting a large number of eligible children.

1.2.2 Epidemiology of UTI

Dr. Alejandro Hoberman studied the prevalence of UTI in febrile infants, using catheterized specimens, in relation to five variables – age, sex, race, temperature, and the presence of an apparent source of fever. Overall, 945 febrile infants were enrolled; urine cultures were positive in 50 (5.3%). Prevalence did not vary with age but was higher among females than males and was higher among white infants than African-American infants. White females with temperature ≥39° C were at particularly high risk (prevalence = 17%). UTI was more prevalent among infants with no identified source of fever than among infants with a possible source of fever, and least prevalent among those with an unequivocal source of fever. The 945 infants enrolled in the study during a 1-year period represented approximately 50% of all febrile infants seen in the Children's Hospital Pittsburgh Emergency Department (CHP-ED) during that time frame.[73]

Dr. Kathy Shaw and colleagues conducted a similar prevalence study[74] in febrile infants presenting to the CHOP Emergency Department (CHOP-ED). They showed that uncircumcised males and Caucasian females under age 2 years with high fever for 2 or more days were most at risk for UTI, especially if there was no other definite source for their fever. This prevalence study was conducted on 2,411 febrile infants in the CHOP-ED where capture rate for the prospective study was 83%. Both CHP and CHOP have mechanisms in place for this ancillary study to duplicate the case finding methods that were used to recruit large numbers of infants and children with febrile UTIs in the emergency department for these prevalence studies.

Having established DMSA scans as the most sensitive imaging modality for detection and localization of experimental acute pyelonephritis, **Drs. Rushton, Majd** and colleagues conducted a prospective clinical study of 94 consecutive children with febrile UTIs to describe the epidemiology of acute pyelonephritis.[45] All children were evaluated with a DMSA scan within 72 hours of diagnosis and cystography was performed within 10 days. Acute parenchymal inflammation was present in 62 of 94 (66%) of patients. Clinical and laboratory parameters were not predictive of DMSA renal scan findings. Only 37% of DMSA scan positive patients were found to have vesicoureteral reflux. When reflux was present, 79% of the patients had DMSA scan findings of acute pyelonephritis, including all patients with Grade III or higher vesicoureteral reflux. In contrast, 60% of patents without demonstrable reflux had findings of acute pyelonephritis on DMSA renal scans. This was one of the earliest studies to show that DMSA scan proven pyelonephritis occurs more often in children without vesicoureteral reflux than in those who do demonstrate reflux.

Subsequent prospective studies by **Rushton, Majd** and colleagues documented that the acute inflammatory changes seen on DMSA renal scans resolve after prompt treatment with antibiotics in approximately 60% of cases, with the remaining 40% developing new renal scarring.[7] New renal scarring occurred equally as often in kidneys without vesicoureteral reflux (43%) as in those with vesicoureteral reflux (40%). They found that the sites of renal scarring corresponded exactly to the sites of acute pyelonephritis, providing convincing clinical confirmation of the primary role of renal parenchymal infection in the etiology of renal scarring, both in the presence and absence of vesicoureteral reflux. These landmark findings were subsequently confirmed by other prospective clinical trails as summarized in a review of the literature by **Rushton.**[75]

More recently, **Pohl, Rushton, Majd** and colleagues prospectively evaluated the incidence of new DMSA scan acute renal inflammatory changes in children with vesicoureteral reflux

on antibiotic prophylaxis who developed febrile breakthrough urinary tract infections. This study demonstrated a relatively low incidence of only 17% of patients who demonstrated new inflammatory renal parenchymal changes on DMSA scans at the time of the breakthrough UTI.[76]

Rushton, Majd and associates also reported a strong correlation between DMSA scan proven pyelonephritis and the uncircumcised foreskin in infant boys with febrile UTIs.[77] The circumcision status of 24 consecutive infant boys hospitalized with acute febrile UTIs was compared with a control group of 63 consecutive male infants hospitalized with an acute upper respiratory infection during a similar time period, comparing circumcision status, type of medical insurance, and racial/ethnic group. There was no statistical difference in race/ethnicity or socioeconomic status (as indicated by type of health insurance) between the two groups. However, 92% of the febrile UTI group was uncircumcised compared to only 44% of the upper respiratory infection control group ($p<0.001$).

1.2.3 Diagnosis of UTI

As part of his first prevalence study, **Hoberman** documented the limitations of the routine urinalysis (UA) to identify young children with UTI (Table 2).

Table 2. Test properties of pyuria and bacteriuria on UA

Criteria	Sensitivity	Specificity	PPV	NPV
≥ 5 WBC/hpf	54	96	45	97
Any bacteria/hpf	86	63	11	99

The poor positive predictive value of the "*standard*" UA, prompted consideration of a new protocol for the performance of UA ("*enhanced*" UA). Borrowing from a protocol developed for adult women with dysuria, an uncentrifuged urine specimen is evaluated and WBCs are enumerated per cubic millimeter (mm^3) using a Neubauer hemocytometer. Results of the standard *vs.* enhanced UA were compared for 698 catheterized urine specimens. This study confirmed that the new method predicted UTI with a high degree of certainty (Table 3).[78]

Table 3. Test properties of enhanced v. standard UA

	Enhanced	Standard UA	P
Sensitivity	**84.5**	**65.6**	**<.05**
Specificity	99.7	99.2	NS
PPV	**93.1**	**80.8**	**<.05**
NPV	99.3	98.4	NS

In a cross sectional concordance study of earlier enrolled and other infants, **Shaw** and colleagues studied 3,873 children to determine which tests are best for predicting UTI.[79] In this and several other publications relating to optimal testing strategies for children with UTI,[74, 79-81] she demonstrated that the urine dipstick plus a urine culture obtained by urethral catheterization is the most cost effective method for screening for UTI, but that the enhanced urinalysis is a more sensitive test that should be reserved for the febrile neonate as there is a high false positive rate. The standard microscopic urinalysis is more costly and adds little information. As a result of these studies, many hospital laboratories will not perform a routine urinalysis if the urine dipstick is negative and the enhanced urinalysis is used for babies in the first two months of life.

Working with Dr. Mark Gorelick **Dr. Shaw** also developed[82] and prospectively validated[83] a clinical prediction rule for identifying febrile girls under age 2 years in the emergency department who are at risk of having a UTI. That clinical prediction rule showed that if two or three of a set of 5 clinical predictors are present, one should screen for UTI. Dr. Shaw will share her expertise in clinical prediction rule development with Dr. Keren to develop the clinical prediction rules outlined in the protocol.

Hoberman and colleagues have also performed research to define pediatric standards for pyuria and bacteriuria in urine specimens obtained by catheter from young febrile children. UA and urine culture results of 2181 catheterized specimens from young febrile children were analyzed to determine a) an optimal bacterial colony count that was clinically "significant"; b) the accuracy of leukocyte esterase and nitrite tests for identifying pyuria and bacteriuria; and c) the ability of pyuria (defined as $\geq$10 WBC/mm^3) to discriminate UTI from asymptomatic bacteriuria (ABU). Urine specimens with 1,000-49,000 CFU/mL were more likely to yield Gram-positive or mixed organisms than specimens with $\geq$50,000 CFU/mL. A count of <10 WBC/mm^3 was almost invariably associated with a sterile culture; a count of $\geq$10 WBC/mm^3 was found in 91% of children with $\geq$50,000 CFU/mL. The dipstick leukocyte esterase test had a sensitivity of 52.9% for detecting $\geq$10 WBC; the dipstick nitrite test had a sensitivity of 31.4% for detecting bacteriuria ($\geq$50,000 CFU/mL). APN was diagnosed using DMSA renal scans in 50 (77%) of 65 children with $\geq$10 WBC/mm^3, but in none of 5 children with <10 WBC/mm^3 (P<.01). They concluded that, for catheterized urine specimens, the presence of both $\geq$10 WBC/mm^3 and $\geq$50,000 CFU/mL almost always discriminated between true UTI, bacteriuria due to contamination and ABU. Definitions validated in this preliminary study to diagnose UTI are used in RIVUR and the proposed ancillary study.[84]

1.2.4 Treatment of UTI

The availability of oral antibiotics with excellent activity against Gram-negative organisms and interest in cost-containment prompted **Hoberman** and colleagues to evaluate, in a multicenter, randomized, clinical trial, the efficacy of oral vs. IV therapy in 306 children 1-24 months with fever and UTI, in terms of short-term clinical outcomes (sterilization of the urine and defervescence) and long-term morbidity (reinfection and incidence/extent of renal scarring 6 months later). Children received either oral cefixime for 14 days or IV cefotaxime for 3 days followed by oral cefixime for 11 days. Consent rate for participation in the study was approximately 90%. The demographic composition of subjects in this trial was almost identical to that of subjects enrolled in the original prevalence study. No differences were noted between oral and intravenous treatment (Table 4). Among children with VUR, renal scarring 6 months later was noted in 15% of cases.

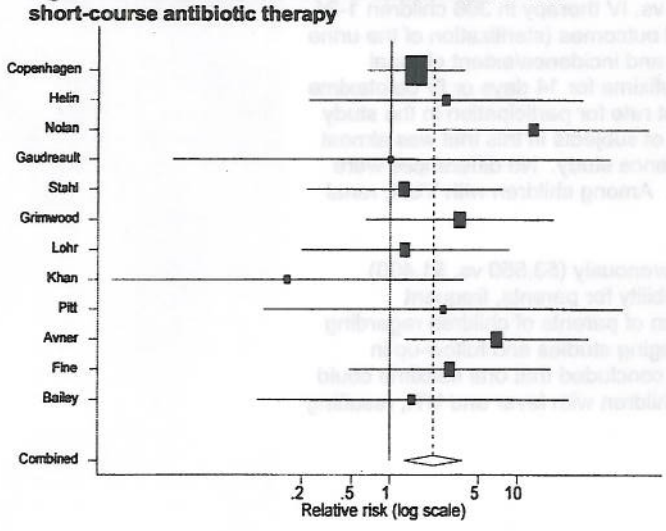
Mean costs were 2.5 fold higher for children treated intravenously ($3,550 vs. $1,400) compared with those treated orally. Their 24-hour availability for parents, frequent interactions with primary care providers and the education of parents of children regarding severity of the condition resulted in the completion of imaging studies and follow-up in approximately 90% of children entered in the trial. They concluded that oral cefixime could be recommended as a safe and effective treatment for children with fever and UTI, resulting in substantial reductions of health care expenditures.[85]

Table 4. IV v. PO antibiotics for UTI trial

Clinical Course	Oral Therapy (N=153)	Intravenous Therapy (N=153)	P
	PERCENT		
Short-term			
Sterile 24 hr. urine culture	100	100	NS
Defervescence (hr., mean)	25	24	NS
Long-term			
Reinfection	4.6	7.2	NS
Renal scarring at 6 months	9.8	7.2	NS
Children with APN at entry			
Renal scarring (95% CI)	16.9 (9.1-24.6)	13.6 (6.1-21)	NS
Extent (% parenchyma)	7.9	8.6	NS

Despite multiple small randomized, controlled trials (RCTs) showing no difference in efficacy between short-course (3 days) and long-course (7–14 days) therapy in children, concerns about occult pyelonephritis and renal scarring have prompted standard recommendations of 7 to 14 days of antibiotics for UTIs in children. To determine whether long-course antibiotic therapy is more effective than short-course therapy for the treatment of UTIs in children, **Dr. Ron Keren** and Dr. Eugenia Chan meta-analyzed 16 RCTs comparing short-course (≤3 days) and long-course (7–14 days) outpatient therapy for acute UTI in children age 0 to 18 years (Figure 3). They found that the pooled estimate for the relative risk (RR) of treatment failure with short-course antibiotic therapy was 1.94 (95% confidence interval [CI]: 1.19–3.15) and for the RR of reinfection was 0.76 (95% CI: 0.39–1.47). When they excluded the 3 studies that did not attempt to restrict their participants to patients with lower UTI, the pooled RR of treatment failure was 1.74 (95% CI: 1.05–2.88) and of reinfection was 0.69 (95% CI: 0.32–1.52). For the subgroup of studies comparing single-dose or 1-day therapy to long-course therapy, the pooled RR of treatment failure was 2.73 (95% CI: 1.38–5.40) and of reinfection was 0.37 (95% CI: 0.12–1.18). For the subgroup of studies comparing 3-day therapy to long-course therapy, the pooled RR of treatment failure was 1.36 (95% CI: 0.68–2.72) and of reinfection was 0.99 (95% CI: 0.46–2.13). They concluded that long-course therapy was associated with fewer treatment failures without a concomitant increase in reinfections, even when studies including patients with evidence of pyelonephritis were excluded from the analysis. These results provided evidence supporting the current

Figure 3. Pooled relative risk of treatment failure with short-course antibiotic therapy



practice and standard for the proposed study of treating pediatric UTIs with 7-14 days of antibiotics.[86]

In a study of 207 patients with neuropathic bladders secondary to spina bifida managed with clean intermittent catheterization, **Rushton, Majd** and colleagues reported that 176 (85%) had one or more episodes of asymptomatic bacteriuria and 72 (35%) had one or more febrile episodes associated with positive urine cultures.[87] Biannual DMSA scans detected 54 new scarring episodes in 42 patients. Logistic regression analysis revealed that factors associated with scarring were febrile infections (adjusted odds ratio (OR) = 30.6, 95% CI = 9.8-95.8; age more than 20 years (OR = 4.3,CI =1.01-18.5); the presence of bladder trabeculation (OR 2.7, CI = 1.0-7.6); and vesicoureteral reflux (OR = 58.8, CI = 6.3 – 547.3). They concluded that asymptomatic bacteriuria in the absence of vesicoureteral reflux was not associated with new renal scarring in patients with neuropathic bladders being managed by clean intermittent catheterization and therefore does not require antibiotic therapy.

Pohl, Majd, Rushton and colleagues have investigated the mitigating effect of adjunctive oral corticosteroids in conjunction with antibiotics versus antibiotics alone when used to treat acute pyelonephritis in the refluxing piglet model.[88] Follow-up DMSA renal scans were used to determine which kidneys progressed to irreversible renal scarring. Acute pyelonephritic lesions were classified as mild (Grade I), moderate (Grade II), or severe (Grade III) based on the volume of renal parenchyma with diminished uptake of DMSA on renal scans performed during the acute infection. They demonstrated a reduced incidence of renal scarring in kidneys with Grade III severe pyelonephritis treated with adjunctive corticosteroids and antibiotics. In piglets with mild or moderate acute pyelonephritis treatment with antibiotics alone was equally effective to combination therapy in preventing subsequent renal scarring.

Pohl, Rushton and colleagues have also evaluated parental preferences in the management of vesicoureteral reflux, looking at treatment modalities of continuous antibiotic prophylaxis, endoscopic therapy, or open surgical correction.[89] In this study, the majority of parents initially opted for antibiotic prophylaxis. After 3 years of treatment, the majority of parents chose endoscopic treatment over antibiotic prophylaxis. When open surgery was included as an alternative to antibiotic prophylaxis, the majority of parents did not choose this until after 5 years of antibiotic prophylaxis.

1.2.5 Evaluation of UTI

Table 2. Findings on Voiding Cystourethrography in 302 Febrile Children with a First Urinary Tract Infection.*

Finding	No. of Children (%)
Normal	185 (61.3)
Vesicoureteral reflux	
Grade I	25 (8.3)
Grade II	42 (13.9)
Grade III	45 (14.9)
Grade IV	5 (1.7)
Grade V	0

* Cystourethrography was not performed in seven children.

Table 5. N Engl J Med 2003; 348:195-202.

Using data from their RCT of PO vs. IV antibiotics for UTI, **Hoberman** and colleagues challenged current thinking about the routine imaging of children following a first febrile UTI. In that clinical trial US and DMSA renal scans were performed to determine the presence of anatomic abnormalities and scintigraphic evidence of APN, respectively. Radiographic VCUG was performed 1 month later to determine the presence of VUR; a repeat renal scan was done 6 months later to determine the incidence

and extent of scarring. US results were normal in ~90% of children; of the abnormalities identified, none modified management of any patient. APN was diagnosed in 61% (187/306) of children based on initial DMSA scan. The extent of parenchymal involvement among patients with APN was 31%. Approximately 40% of children had VUR, most classified as Grades I to III (Table 5). Repeat scans were performed in 272/306 (88%) children, with renal scarring (mean ~8% of the renal parenchyma) noted in 26/272 (9.5%) children. Approximately 15% of children with APN at study entry had renal scarring 6 months later. VUR was the only clinical characteristic significantly associated with a higher likelihood of renal scarring (Figure 4). They concluded that in the clinical management of young children with first diagnosed UTI, US and renal scans performed at the time of acute illness were of limited value. VCUG was useful for identifying children with VUR if it could be proven that they benefit from prophylactic antimicrobial therapy. Renal scans performed 6 months later were useful in identifying children with scarring who might benefit from the performance of urine cultures in subsequent febrile illnesses.[6]

Figure 4. N Engl J Med 2003; 348:195-202.

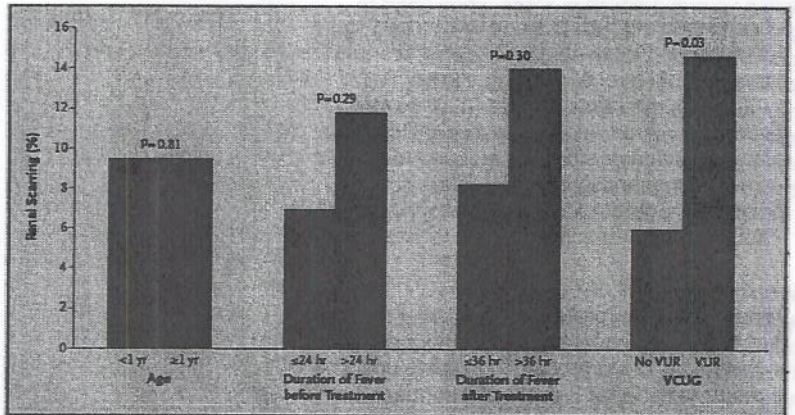


Figure 3. Presence or Absence of Renal Scarring after Six Months According to Demographic and Clinical Characteristics of Children with a First Urinary Tract Infection.
VUR denotes vesicoureteral reflux, and VCUG voiding cystourethrogram.

Hoberman and colleagues have also validated the intra- and interobserver reliability in the interpretation of DMSA renal scans, performed to evaluate the presence of renal parenchymal inflammation or scars, using a standardized rating scale. Two-experienced nuclear medicine physicians reviewed 63 DMSA scans independently, blindly and in random order on two occasions. Kidneys were divided into four regions and photopenia in each of these regions was assessed. Contours were assessed visually as scars or inflammatory lesions, and the percentage of kidney involvement determined. High levels of intra- and interobserver agreement were reported.[90] The same methods will be used to validate the renal scarring grading scale developed for the RIVUR and this ancillary study.

Drs. Rushton, Pohl, and Majd have conducted numerous studies related to the diagnosis and imaging of acute pyelonephritis and renal scarring. **Rushton and Majd** and colleagues initially described the correlation of DMSA renal scan findings with the histopathologic findings of pyelonephritis in the refluxing piglet model.[64] Typical findings of acute

pyelonephritis included areas of diminished uptake of DMSA with preservation of the renal contour. The DMSA scan was found to be highly sensitive and reliable for the detection and localization of experimental acute pyelonephritis with a sensitivity of 89% and specificity of 100%. When individual pyelonephritic lesions were analyzed, DMSA scan findings correlated with histopathologic findings in 62 of 66 renal zones for an overall agreement rate of 94%. Lesions not detected were microscopic foci of inflammation not evident on gross examination and not associated with significant parenchymal damage.

In another study, **Majd, Rushton** and colleagues compared SPECT and pinhole imaging of DMSA renal scans for the detection and localization of acute pyelonephritis in piglets with bilateral vesicoureteral reflux of infected urine. The sensitivity and specificity for detection of kidneys with pyelonephritis was 87% and 100% respectively for pinhole imaging and 96% and 71% respectively for SPECT.[91] The overall agreement for the presence or absence of kidney involvement was 90% for both. Subsequent animal model studies by **Majd, Pohl and Rushton** compared the diagnosis of acute pyelonephritis using multiple modern imaging modalities, including SPECT DMSA scans, spiral CT, gadolinium-enhanced MRI, and power Doppler sonography.[92] The sensitivity and specificity for the detection of experimental acute pyelonephritis in 210 renal zones (70 kidneys) was 94% and 96% for SPECT DMSA; 91% and 93% for MRI; 88% and 94% for spiral CT; and 56% and 81% for power Doppler sonography. This study confirmed DMSA as the gold standard for detection and localization of acute pyelonephritis.

1.2.6 Treatment of VUR

Dr. Douglas Canning has conducted important research on the use of endoscopic injectables and the endoscopic correction of vesicoureteral reflux,[93-95] and has also been involved in neuroanatomical basic science research looking at the neurological innervation of the trigone and bladder base.[96, 97] Together with a series of surgical colleagues during his training, he developed and documented a new technique for the correction of vesicoureteral reflux in patients with exstrophy. He also did extensive work experimenting with autologous free fat transplant as a substance to endoscopically correct vesicoureteral reflux.[98, 99] More recently, Dr. Canning collaborated on a cost-effectiveness analysis of endoscopic correction of vesicoureteral reflux in children.[100] The cost data for that study were derived from a long-term observational study of a large cohort of CHOP patients, a seminal study with a 15-year perspective on the spontaneous resolution of vesicoureteral reflux and the morbidity associated with urinary tract infection.[101] Dr. Canning's division, with its considerable volume, has long been a source of patients for large-scale federally sponsored studies. During the first International Reflux Study, the CHOP team, then headed by Dr. John Duckett, recruited more than three-quarters of the North American surgical arm patients.[33] We anticipate that CHOP's Division of Urology will repeat this recruitment effort for the proposed study.

1.3 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). Any episode of noncompliance will be documented.
The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report adverse events in accordance with The Children's Hospital of

Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

~~2.1~~ Specific Aims

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The **Specific Aims** of this study are:

1) **To compare the proportion of children who develop renal scarring 2 years following a first or second episode of UTI among children in the proposed ancillary study who do not have VUR and children in the RIVUR study who do have VUR and are receiving placebo.**

   Hypothesis: The proportion of children who develop renal scarring among children in the ancillary study who do not have VUR and children in the RIVUR study who do have VUR and are receiving placebo will be equivalent (<10% absolute risk difference).

2) **To develop a prediction rule that accurately identifies children at high risk of developing renal scarring as well as children with virtually no risk of developing renal scarring following a first or second episode of UTI.**

   Hypothesis: A prediction rule incorporating clinical and demographic factors associated with renal scarring will predict with >98% sensitivity and >50% specificity which children will develop renal scarring following a first or second episode of UTI. A prediction rule with these test properties would identify nearly all children who develop renal scarring while accurately assessing as low risk at least 50% of children who do not develop renal scarring.

~~2.2~~ Secondary Aims

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The **Secondary Aims** of this study are:

1) **To compare the proportion of children who experience a recurrent UTI following the a first or second episode among children in the proposed ancillary study who do not have VUR and children in the RIVUR study who have VUR and are receiving placebo.**

   Hypothesis: The proportion of children who experience a recurrent UTI among children in the ancillary study who do not have VUR and children in the RIVUR study who do have VUR and are receiving placebo will be equivalent (<10% absolute risk difference).

2) **To develop a prediction rule that accurately identifies children at high risk of experiencing a recurrent UTI as well as children with virtually no risk for recurrence following a first or second episode of UTI.**

   Hypothesis: A prediction rule incorporating clinical and demographic factors associated with renal scarring will predict with >98% sensitivity and >50%

specificity which children will have a recurrent UTI. A prediction rule with these test properties would identify nearly all children who go on to experience UTI recurrence while accurately assessing as low risk at least 50% of children who do not experience UTI recurrence.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

We propose to conduct a multi-center prospective cohort study comparing rates of renal scarring and recurrent UTI after a first or second episode of UTI in 2 groups of children—one group of children who do not have VUR and one group of children who do have VUR and are treated as part of the RIVUR protocol with placebo. All participants will be enrolled over an 18-24 month period and followed for at least 2 years post-enrollment.

3.1.1 Screening Phase

Children with a first or second $_{F/S}$UTI will enter the screening phase of the study (Figure 1), during which their eligibility will be confirmed and baseline studies, including a VCUG and a renal ultrasound will be performed. The initial eligibility criteria for the ancillary study will be identical to those used for the RIVUR study. Children who are found to have Grades I-IV VUR and whose baseline studies do not reveal any exclusion criteria will advance to the randomization phase of the RIVUR study. Children whose VCUGs do not demonstrate VUR will be invited to enroll in the proposed ancillary study. In all cases the DMSA scan will be performed within 112 days (16 weeks) of the index UTI, but no longer than 2 weeks after the date of study enrollment. From previous observational studies with children of this age group with febrile UTIs, a 50-75% consent rate is expected. Retention is expected to be high due to the involvement of investigators at the time of acute illness and telephone calls every 2 months. An attrition rate of 10% is expected throughout the 2-year follow-up period.

3.1.2 Eligibility and Screening Data

3.1.2a Renal/Bladder Sonogram

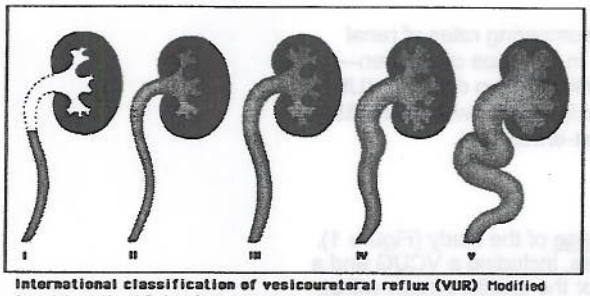
All children will be evaluated within 16 weeks (112 days) of diagnosis of the index UTI with a renal/bladder sonogram. This study is performed as **standard care** in all young children diagnosed with a first or second UTI to screen for obstruction or other anatomic abnormalities of the urinary tract, such as ureteropelvic junction obstruction, a posterior urethral valve, or hydronephrosis associated with an ectopic ureter or ureterocele. The renal/bladder sonogram will be completed prior to recruitment as part of clinical care and not as part of the research study.

3.1.2b Voiding Cystourethrogram (VCUG)

A contrast VCUG will be obtained within 16 weeks (112 days) of diagnosis of the index UTI. This study is conducted as **standard care** in all young children diagnosed with a first or second UTI to identify and grade the severity of VUR. Morphological abnormalities of the bladder and the appearance of the urethra will be noted. VUR will be graded according to the five-grade system of the International Reflux Study Group[102] (Figure 5): Grade I, reflux into ureter only; Grade II, reflux into ureter, pelvis and calyces without dilation; Grade III, mild to moderate dilation and/or tortuosity of the ureter and moderate dilation of the renal

pelvis but little or no blunting of the fornices; Grade IV, moderate dilation and/or tortuosity of the ureter and moderate dilation of the renal pelvis and calyces; and Grade V, gross dilation and tortuosity of the ureter and gross dilation of the renal pelvis and calyces. The VCUG will be completed as part of clinical care prior to recruitment into the study and not as part of the research study.

Figure 5: International classification of vesicoureteral reflux (VUR)



International classification of vesicoureteral reflux (VUR) Modified from International Reflux Committee. Medical versus surgical treatment of primary vesicoureteral reflux. Pediatrics 1981; 67:392.

3.1.2c Treatment for the Index UTI

Children diagnosed with first or second febrile or symptomatic UTI in the screening phase of the study will have to receive appropriate treatment for the index UTI episode. In all instances, this will require treatment for a minimum of 7 days with an effective drug for the causative organism. If adequate susceptibility is documented, a repeat urine culture demonstrating test of cure will not be obtained.

Children who meet eligibility criteria and whose parents consent to participate in the study will advance to the observation phase.

3.2 Study Duration, Enrollment, Number of Sites and Project Management

3.2.1 Duration of Study

All participants will be enrolled over an 18-24 month period and followed for at least 2 years post-enrollment.

3.2.2 Timeline for Subject Enrollment

The timeline for subject enrollment is summarized in Table 6. Children recruited for the ancillary study will be those who are screened for the parent RIVUR study but are found not to have VUR. Therefore, enrollment for the ancillary study will be concurrent with the parent study. The parent study began enrollment in June of 2007 and will enroll children for 18-24 months, depending on enrollment rates. We plan to begin enrollment in October 2007 and finish enrollment in March 2009, three months before enrollment for RIVUR is completed. The numbers in the timeline assume a 10% loss to follow-up per year.

Table 6. Timeline for Subject Enrollment

	Year 1				Year 2				Year 3				Year 4				Year 5			
	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Nov	Oct-Dec	Jan-Mar
	2008			2009				2010				2011				2012				2013
RIVUR Enrollment																				
Baseline visit (n=360)	60	60	60	60	60	60														
6 Month Visit			60	60	60	60	60	60												
12 Month Visit (n=320)					54	54	54	54	54	54										
18 Month Visit							54	54	54	54	54	54								
24 Month Visit (n=288)									49	49	49	49	49	49						
Close database and database reconciliation															X	X				
Analysis and Manuscript Preparation																	X	X	X	

3.2.3 Total Number of Study Sites/ Total Number of Subjects Projected

Participants will be recruited from 3 study sites:

1) The CHOP Healthcare Network, which includes the wards of the Main Hospital, the Emergency Department, the Radiology Department, 6 Urology Practices, and 33 primary care practices sharing a common electronic health record in the CHOP Healthcare Network. The outpatient practices of the CHOP Healthcare Network span a large geographic area and provide a wide array of primary care and sub-specialty services. In FY 2004 the CHOP Healthcare Network saw a total of 987,342 outpatient visits. CHOP's four primary care centers and one faculty practice provide health services to more than 20,000 area children. The Hospital has also established a network of 28 regional pediatric practices in Pennsylvania, New Jersey, and Delaware called "Kids First," with 153 physicians and total patient panels exceeding 74,000 covered lives. All 33 of these primary care practices are members of a Practice Based Research Network and share a common electronic health record (EPIC).
2) The CHP Healthcare Network, which includes the Primary Care Center (22,300 visits annually), the Emergency Department (60,000 visits annually), 18 suburban affiliated community pediatric sites, the Division of Pediatric Urology, and the hospital wards at CHP.
3) The CNMC Healthcare Network, which includes five Children's Health Centers and five subspecialty Outpatient Centers located throughout the Washington-metro area, as well as the Emergency Department and hospital wards at CNMC.

The RIVUR protocol stipulates that CHOP and CHP each enroll 120 subjects into the RIVUR study. We anticipate that CNMC, which is part of a larger network of centers in the RIVUR study (represented on the steering committee by Women and Children's Hospital of Buffalo) will contribute 60 subjects to RIVUR. If randomization results in half of these 300 subjects receiving placebo, then there will be 150 subjects from these 3 study sites in the placebo arm of RIVUR.

The participants in the proposed ancillary study will serve as the comparison group. Each of the sites intends to enroll 120 subjects for a total of 360 subjects in the comparison group. This should not be problematic, even if the study's enrollment period does not overlap completely with RIVUR's, because among children who have had a UTI, approximately 60-70% will not have VUR, so non-refluxing children will outnumber refluxing children by at least 2.5:1. Furthermore, there will be fewer disincentives to enrollment in the ancillary study, as it is observational in nature, involves and does not include randomization to a placebo. For these reasons, we do not anticipate difficulty enrolling 120 subjects per site, even with an anticipated start date up to 1 year into RIVUR's enrollment period.

Combining placebo treated participants from RIVUR and participants in the ancillary study, our sample size will be 510 (150 from RIVUR and 360 from the ancillary study). If, as described in the "Background and Significance" section (1.1), approximately two-thirds of enrolled children will have pyelonephritis and 15-52% of them will develop scars from the index UTI, then approximately 10-35% of children (n=51 to 179) will have some renal scarring during the 2-year study period. This does not take into consideration renal scarring that will develop from recurrent UTIs, which will only serve to increase the proportion of children who have renal scarring at the end of 2 years.

3.2.4 Project Management

3.2.4a Leadership at Participating Sites

Drs. Keren, Hoberman, and Pohl (from CHOP, CHP, and CNMC, respectively) will serve as site directors at each of their institutions and will develop and implement all policies, procedures and processes and provide oversight of the research protocol. In these roles, they will be responsible for the implementation of the scientific agenda and will ensure that systems are in place to guarantee institutional compliance with US laws, DHHS and NIH policies including biosafety, human research, data and facilities. Dr. Keren will be the Principal Investigator on the grant and in this role will assume responsibility for overall administrative grant management, including maintaining communication among co-investigators and key personnel through monthly meetings, communication with NIH, and submission of annual reports. As site directors at each of their respective institutions, Drs. Hoberman and Pohl will be responsible for his own fiscal and research administration as outlined in the subcontracts established in preparation for the grant proposal. If either of them moves to a new institution, attempts will be made to transfer the relevant portion of the grant to the new institution. In the event that they cannot carry out their duties, a new co-investigator will be recruited as a replacement.

3.2.4b Steering Committee

The site directors, along with Dr. Carpenter from the Data Coordinating Center, will be members of the Steering Committee for the study. The Steering Committee will communicate once to twice a month, either by phone or in person, to discuss experimental design, data analysis, and all administrative issues. They will work together to discuss any changes in the direction of the research projects and the reallocation of funds, if necessary. The steering committee will also make decisions regarding the involvement in the ancillary study of other sites participating in the parent study (RIVUR) (Figure 6).

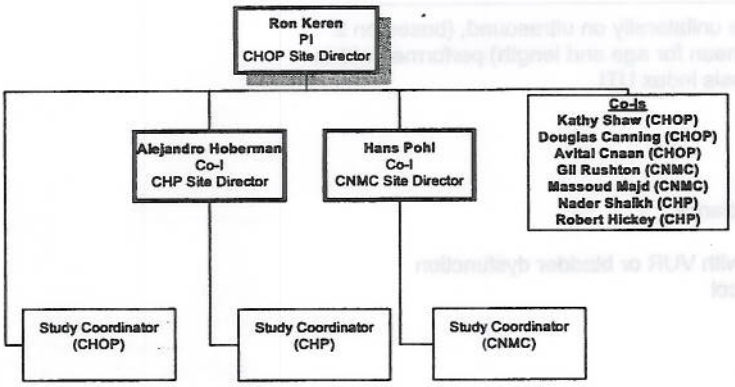


Figure 6. Organizational Chart

3.3 Study Population

This study will enroll approximately 360 children 2-72 months of age. Children of both genders and any race/ethnicity who receive care in the healthcare networks of the study sites will be considered for enrollment. Parents of eligible children will be invited to participate in the study based on the diagnosis of a first or second UTI. Children for whom parents provide consent will be evaluated with a renal ultrasound, VCUG and DMSA scan within 16 weeks of the UTI. The ultrasound and VCUG are routine and the DMSA is increasingly used to evaluate children with UTI. This study will enroll only children, who may be considered a vulnerable population.

3.3.1 Inclusion Criteria

1) Age at enrollment 2-72 months. Note that children as young as 1 month may be screened for study.
2) Diagnosed first or second $_{F/S}$UTI within 120 days (16 weeks) prior to enrollment
3) Appropriately treated first or second $_{F/S}$UTI
4) Parental/guardian permission (informed consent) and if appropriate, child assent.

3.3.2 Exclusion Criteria

1) For children less than 6 months of age at randomization, gestational age <34 wks
2) UTI diagnosis more than 112 days (16 weeks) prior to enrollment
3) Index UTI not appropriately treated
4) VUR (Grades I-V) diagnosis by VCUG
5) Co-morbid urologic anomalies
   - Hydronephrosis, SFU Grade 4
   - Ureterocele
   - Urethral valve
   - Solitary kidney

- Profoundly decreased renal size unilaterally on ultrasound, (based on 2 standard deviations below the mean for age and length) performed within 112 (16 weeks) days of diagnosis index UTI
- Multicystic dysplastic kidney
- Neurogenic bladder
- Pelvic kidney or fused kidney

6) History of other renal injury/disease
7) Congenital or acquired immunodeficiency
8) Complex cardiac disease
9) Any known syndromes associated with VUR or bladder dysfunction
10) Unable to complete the study protocol
11) Unlikely to complete follow-up

3.3.3 Comparison Group from RIVUR Study

1.) Inclusion: Subjects enrolled in RIVUR study and randomized to placebo.
2.) Exclusion: RIVUR subjects that have not agreed to future use of their data.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures

3.3.4 Inclusion of Women and Minorities

We plan to recruit and enroll children that are representative of the gender, racial, and ethnic distribution of children with UTI in the Healthcare Networks of CHOP, CHP, and CNMC. Table 7 summarizes the projected sex and ethnic distribution of children that we will enroll in the study. It is based on the distributions observed among children diagnosed with UTI during a 2-year time period at the three participating study sites (weighted by site).

Table 7. Sex and ethnic distribution of target population

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	White	Total Racial	Hispanic or Latino	Not Hispanic or Latino	Total Ethnic
Female	1%	3%	26%	49%	79%	8%	71%	79%
Male	0%	1%	8%	13%	21%	3%	18%	21%
Total	1%	4%	34%	62%	100%	11%	89%	100%

4 STUDY PROCEDURES

4.1 Baseline DMSA Renal Scans

All children enrolled in the study will have a DMSA scan within 2 weeks following enrollment and no more than 16 weeks (112 days) of the index UTI to determine the presence of APN or pre-existent renal scarring. Children will be injected with a dose of 5 mCi ^{99}TcDMSA per 1.73 m^2 body surface area (minimum dose 1 mCi). High-resolution

magnified images of the kidney will be obtained, including posterior and both right and left posterior oblique projections using a gamma-camera-computer system equipped with a high resolution parallel collimator, between 2-4 hours following injection. Right to left relative function will be calculated by the ratio of right kidney to left kidney counts obtained from the posterior views after background correction. The results will be described quantitatively as the percentage uptake in the right kidney vs. left kidney. Absolute uptakes will not be obtained. Cortical defects at this early DMSA will be defined as focal or diffuse decreased uptake of DMSA with/without loss of contours or cortical thinning with decreased volume. Using criteria established by Majd, defects will be classified as APN or pre-existent renal scarring.[64, 91] These cortical defects will be assessed semi-quantitatively by dividing the renal cortex into 12 equal segments (Figure 7). The number of renal parenchyma segments affected will be determined and the grade of scarring will be assigned based on a grading system developed by the Imaging Committee of the RIVUR study during development of that protocol.

Figure 7. Grading system for characterizing extent of renal scarring

Grade	Description
1	1-2 kidney segments affected
2	3-4 kidney segments affected
3	>4 kidney segments affected
4	Global atrophy characterized by a diffusely scarred and shrunken kidney.

These evaluations will be made by two reference nuclear medicine investigators employed through the RIVUR study, including Dr. Majd at CNMC. The standardized grading systems will be used by the reference nuclear medicine investigators without knowledge of clinical events or treatment arm. Final diagnosis of disagreements in interpretations will be reconciled by consensual diagnosis. The process for interpreting DMSA scans has been validated (inter and intra-observer reliability measured) and improved as part of an imaging pilot for the RIVUR study.

4.2 Baseline Evaluation

Information on the following potential predictors and confounders of renal scarring and recurrent UTI will be collected during the baseline evaluation:

1) **Demographic information** on sex, race, ethnicity, age, sibling order, parental education, and income will be collected.
2) **History of index UTI** including type and duration of symptoms prior to antibiotic treatment, highest documented temperature at presentation, documented physical exam findings, antibiotic choice and duration of therapy.
3) **Past medical history** including regular medications and chronic conditions will be collected. There will be an age-appropriate evaluation for dysfunctional voiding symptoms based on the Dysfunctional Voiding System Score developed by Farahat et al[1], and an assessment for constipation using definitions published by the Paris Consensus on Childhood Constipation Terminology (PACCT) Group.[2]

4) **Family history** of VUR, UTI, renal scarring, and kidney disease will be collected.
5) **Entry examination** will include a general physical examination, blood pressure, height or length, and weight.
6) **Laboratory data** from the index UTI will be abstracted from medical records. These include infecting organism and its sensitivity/resistance pattern, information about inflammatory markers, such as peripheral white blood cell count, neutrophil percentage, erythrocyte sedimentation rate, and C-reactive protein.
7) **Baseline blood** will be collected and tested for serum creatinine, and Cystatin C (using the same central laboratory as the RIVUR trial). Additional blood will be collected, stored and shipped to the NIH Biosample and Genetics Repositories for future studies.
8) **Baseline urine** will be collected, stored and shipped to the NIH Biosample Repository for future studies.
9) A **quality of life** instrument will be administered and a parent diary will be distributed.

All data will be entered in electronic case report forms (eCRFs). Optional paper CRFs will be available.

4.3 Monitoring and Evaluations During Subsequent Episodes of Fever

Parents will be educated at the time of their child's enrollment in the study about the potential sequelae of untreated UTI and the benefits of prompt and adequate treatment. They will be instructed to (1) contact primary care providers and study personnel in the event of intercurrent febrile illness, (2) have their child evaluated within 24-48 hours and (3) have a urine specimen obtained to evaluate for the presence of UTI. Additionally, a recent history of fever or other signs or symptoms compatible with UTI will be identified by information obtained during study-initiated phone calls every 2 months. The research nurse or the PI at each participating site will be available to parents of enrolled children via a study-dedicated cellular phone or hospital-based beeper. Primary care providers will be reminded through regular communication and letters about their patient's participation in the study. Specimens for culture will be obtained at the time of febrile illnesses and when children have symptoms localized to the urinary tract. Stringent criteria for recurrent UTI will be identical to those used at study entry. Children with reinfections will be treated with effective antimicrobial therapy as outlined previously and will continue in the study until they complete the study protocol or develop a degree of renal scarring or number of reinfections used in the RIVUR protocol to define treatment failure.

4.4 Phone Contact and Routine Follow-up Visits

Following the protocol established for the parent RIVUR study, parents will be contacted by phone or email every 2 months to ascertain intercurrent illnesses, and children will be seen at routine follow-up visits at 6, 12, 18 and 24 months. The target date of these visits or phone interviews will be determined by the date of enrollment. All interviews and clinic exams will be conducted within 10 days of the target date. If the follow-up schedule must be changed due to illness, geographic relocation or extended vacation, procedures will be followed to document the change in schedule. If a patient misses an appointment, a study

coordinator will contact his/her family by phone or mail to inquire about intercurrent illness. At each study visit an interim history and physical examination will be performed. Dysfunctional voiding will be assessed at the 12 and 24 month visits. Parent diaries will be reviewed at each study visit and quality of life questionnaires will be completed at the 12 and 24 month visits. Measurement of serum creatinine and cystatin-c and urine microalbumin/creatinine will be repeated at the 24-month visit. Urine and blood specimens will be collected again at the 24-month visit for submission to the NIDDK Biosample and Genetics repositories.

4.5 Outcome DMSA Scan

Outcome DMSA renal scans will follow the same procedures and standards of the baseline scan. In general participants will have the outcome DMSA scan performed 24 months after the index UTI. For safety reasons, we will use the criteria developed to define treatment failure for the RIVUR study as indications for performance of an early DMSA scan. Therefore, children whose baseline DMSA scan shows minimal or no scarring (grade 2 or less in each kidney) will have their outcome DMSA scan performed early if they experience the occurrence of 2 recurrent $_{F}$UTIs or a total of 4 recurrent $_{F/S}$UTIs within the study period. The outcome DMSA in these children will be performed approximately 4 months after the last UTI that qualified them as a "treatment failure". Children whose baseline DMSA scan shows grade 3 or higher scarring in either kidney will have a repeat DMSA scan performed at the time of any recurrent $_{F}$UTI; if additional renal segment involvement (acute pyelonephritis or renal scarring) is observed, then, an outcome DMSA scan will be performed at approximately 4 months following any $_{F}$UTI. If no additional renal segment involvement is observed, the child will have the outcome DMSA scan performed at 24 months per routine. Finally, children who have a febrile UTI in the first 8 months of the study will have an interim DMSA scan performed at 12 months. If new renal scarring is noted, that child will be considered a treatment failure and the interim DMSA scan will serve as the outcome scan. If a febrile UTI occurs within 8-12 months, the interim DMSA scan will be scheduled 4 months from the interim UTI.

4.6 Indications for Referral to a Pediatric Urologist

For safety reasons, we also will use the criteria developed to define treatment failure for the RIVUR study as indications for referral to a pediatric urologist. Therefore, children whose baseline DMSA scan shows minimal or no scarring (grade 2 or less in each kidney) will be referred to a urologist if they experience occurrence of 2 recurrent $_{F}$UTIs or a total of 4 recurrent $_{F/S}$UTIs within the study period. Children whose baseline DMSA scan shows grade 3 or higher scarring in either kidney will have a repeat DMSA scan performed at the time of any recurrent $_{F}$UTI; if additional renal segment involvement (acute pyelonephritis or renal scarring) is observed, then, in addition to having the outcome DMSA scan at approximately 4 months following the $_{F}$UTI, they will be referred to a pediatric urologist.

4.7 Alert Notification

Primary care providers will be notified of clinically significant findings identified at study follow-up visits.

4.8 Strategies to Promote Adherence and Retention

We will employ a number of retention strategies during the study to promote attendance of subjects in both groups at all follow-up visits. These include a highly trained, competent and consistent staff, flexible scheduling, readily available mass transit, reimbursement for parking on-site, and reimbursement of $50 for measurements completed at baseline and 24 months, and $25 at 6, 12, and 18 months. All families will understand that this is a two-year commitment and we will not enroll families who are unable or unwilling to commit for the entire period. If families unexpectedly move out of the region during the study period, we will make every effort to continue their participation to the measurement visits by compensating for travel costs. Operations will be geared to ease scheduling of the measurement visits and to ensure the comfort and enjoyment of the subjects and parents during all measurements. The schedule of contacts is designed to facilitate participant retention through regular contacts. Parents will be asked to provide contact information for individuals (relatives, friends, co-workers) who would likely know their location in the event the child becomes lost to follow-up. This contact information will be stored locally in a secure location.

4.9 Unscheduled Visits

We will ask participants to notify the study team of any unscheduled visits to their primary care providers or other health care settings for diagnosis and management of urinary tract infections. We will also inquire about and document unscheduled visits to healthcare providers for urinary tract symptoms or infection at the time of the bimonthly phone calls.

4.10 Subject Completion/Withdrawal

Criteria for withdrawal of subjects and plans for provision of care after withdrawal. Example: Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules or AEs. Children who are started on antimicrobial prophylaxis will continued to be followed for the duration of the study period but they will not contribute data to analyses after prophylaxis is begun. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.10.1 Early Termination Study Visit

List the procedures that will be performed for each subject that withdraws prior to completing the study. Example: Subjects who withdraw from the study will have all procedures enumerated for the 24 month visit as the early termination visit.

5 STUDY ENDPOINTS AND EVALUATIONS

5.1 Overview of Primary and Secondary Endpoints

The proportion of children who have any renal scars assessed on the outcome DMSA scan will serve as the principal analysis variable. Secondary endpoints include the proportion of

children with severe scarring, the proportion of children who have at least one recurrent UTI, and the proportion of children who become "treatment failure".

5.2 Primary Endpoint: Renal Scarring

The incidence and extent of renal scarring will be determined 24 months after the index UTI episode using renal scintigraphy (^{99}Tc dimercaptosuccinic acid (DMSA) scan). Children who experience "treatment failure" as defined in the parent study will have the outcome scan approximately 4 months later. Renal scarring will be defined as decreased uptake of tracer associated with loss of contours or cortical thinning. In order to quantify the extent of renal scarring, each kidney will be divided into 12 segments and a five level grading system will be applied (Figure 6). Severe scarring will be defined as the presence of grades 3 or 4 scarring on at least one kidney.

5.3 Secondary Endpoints

5.3.1 Recurrence of UTI

Suspected recurrent UTI events will be reviewed and adjudicated to determine if they meet the RIVUR criteria for a secondary endpoint. The definition of recurrent $_{F/S}$UTI requires the presence of (1) fever or urinary tract symptoms[3], and (2) pyuria based on urinalysis, and (3) culture-proven infection with a single organism. A UTI will be defined as recurrent only if its onset occurs more than 2 weeks from the last day of treatment for the preceding UTI, or following a negative urine culture.

5.3.2 "Treatment Failure"

Although treatment will not be provided as part of this observational study protocol, we will characterize the children in this ancillary study in terms of the criteria used to define treatment failure in the RIVUR study. In any participant, the occurrence of two $_{F}$UTIs **or** a total of four $_{F/S}$UTIs during the study period **or** an interim 12-month scan showing new scarring at a site different from the index APN or worsening scarring evidenced by extension of a preexistent scar seen on the baseline DMSA scan will be classified as a treatment failure. In treatment failure cases where new or worsening scarring is observed on the 12-month DMSA scan, the interim scan may serve as the outcome DMSA scan. Children whose baseline DMSA scan shows grade 3 or higher scarring in either kidney will have a repeat DMSA performed at the time of any recurrent $_{F}$UTI. If additional renal segment involvement is observed in comparison with the baseline scan,, these children will also be categorized as treatment failure and have an outcome DMSA scan at approximately 4 months following the $_{F}$UTI. If no further damage is apparent, they will continue in the study as assigned.

Children whose interim 12-month scan shows new or worsening scarring in comparison to a previous scan will be classified as meeting treatment failure criteria. The interim scan will serve as the outcome DMSA scan in these participants.

[3] Must occur within ± 24 hours of initiating work-up for UTI.

6 STATISTICAL CONSIDERATIONS

6.1 Statistical Methods

6.1.1 General Analysis

The initial analysis will involve describing the distribution of data. The primary exposure of interest is presence or absence of VUR. We will characterize exposed and unexposed subjects by all predictor variables. Categorical variables will be summarized by frequencies while continuous variables will be summarized by mean, median, standard deviation, and range. The purpose of this description is to identify any differences in the exposure groups that may explain differences in renal scarring or recurrent UTI, in addition to presence or absence of VUR. Analyses will need to be adjusted for any differences in these potentially confounding variables. We will also calculate correlations (Pearson or Spearman, depending on whether continuous or ordinal) and associations between the predictor variables. In those cases where there is a strong correlation or association, we will choose variables with more clinical relevance to be the candidate predictor variables for Aims 2 and 4.

6.1.2 Analysis plans for Specific Aim 1 – Primary Outcome

In order to test whether the proportion of children who have renal scarring on DMSA scan is equivalent among the CUTIE study patients who did not have VUR and the placebo-treated RIVUR study who did have VUR, we will calculate the difference in proportions and test whether the difference in proportions is less than 10% or not using a one-sided 0.05 significance level. We will therefore test the null hypothesis that the VUR group and non-VUR group are not equivalent and that the difference in the proportions of renal scarring between the groups is 10% or farther from zero in the same direction. If we reject this null hypothesis, the alternative hypothesis in this case is that the proportions of renal scarring in the two groups are equivalent, closer to each other than a 10% difference. This approach of essentially "reversing" the traditional roles of the null and alternative hypothesis is used to assure that the study is powered to detect equivalence, and not merely to conclude equivalence because differences were not significant on a traditional testing approach [which can occur simply because of a too small sample size]. As a secondary analysis, we will test using the same approach the proportion of children with severe scarring (grades 3 or 4 scarring on at least one kidney). The DMSA is planned to be done at 24 months after the index UTI, but if a DMSA is indicated and done sooner, and shows scarring, that DMSA will serve as the primary outcome.

If the subjects who agree to enroll in RIVUR differ from those who agree to enroll in CUTIE in ways that are associated with the development of renal scarring, then a comparison of renal scarring in these 2 groups will be confounded by these differences. Although a priori we do not anticipate such differences to emerge, in testing for differences in renal scarring we will adjust for potential risk factors for renal scarring (age, race, gender, fever) using multivariable logistic regression models. We will also determine whether the 2 groups are different in terms of other factors not known to be associated with renal scarring, and we will adjust for those factors as well in order to control for any potential unrecognized confounders. If any adjustment is found necessary to prevent bias, then we will also do hypothesis testing based on the 95% confidence interval of the odds-ratio calculated from the coefficient of the VUR variable in the logistic regression model, testing for equivalence as above.

6.1.3 Analysis Plans for Specific Aim 2 – Predictive Model

The primary approach to Aim 2 will be to use a multivariable logistic model-fitting approach. At the first step, all variables identified as predictors will be entered in univariate logistic regression models. Predictor variables that are associated with the outcome at the $p<0.2$ level will be considered as potential predictors/confounders and candidates for inclusion in the full multivariable models.

Multivariable modeling techniques will be used to develop prediction models for the development of renal scarring.[34-36] Clinical judgment and strength of predictive variables in previous studies will force some variables to be included in the models regardless of their level of statistical significance (e.g., VUR grade, age, sex). Potential interaction variables to be considered in the models will be chosen based on the clinical judgment of the investigators and evidence from the literature, if both variables are candidates for inclusion in the model based on the first step.

The multivariable models will be developed using the best subset selection method.[103] The best subset approach starts by fitting all single variable models and examining the log-likelihood of the model. Then all pairs of variables are entered into models and the log-likelihood calculated. The best two-variable models are those with the largest log-likelihood and a significant G^2 statistic for the difference between the two-variable model and the two single-variable models nested in it. The G^2 statistic is calculated as twice the difference in log likelihood between two nested models and has asymptotically a chi-square distribution with degrees of freedom equal to the difference in the number of parameters between the two nested models. The next step consists of examining all three-variable models and comparing those to the two-variable models. The process stops when the G^2 statistic shows that adding variables no longer increases the log-likelihood significantly. The advantage of this process is that it is a comprehensive exploration of all available models, as opposed to the stepwise approach, which only explores the next best variable, and whose path may not lead to the best model. While this process is not feasible if there are too many variables to be explored, in this study, the number of variables is limited and this process therefore can be employed for optimal results. Finally, the process can lead to more than one optimal model (e.g. two or three models with somewhat different variables and comparable log-likelihoods). We will explore the content implications of different models and decide which model is best translated into a practical prediction rule for use in clinical practice. In the process of this modeling we will make sure that at any time an interaction variable is in the model, the two single variables forming the basis for the interaction are also included in the model.

Prediction model performance will be evaluated in terms of (1) discrimination (ability of the model to separate individuals with different outcomes); and (2) calibration, or fit (agreement between observed and expected probabilities).[34, 36] Discriminative ability will be measured using the c index,[36] which is defined as the proportion of all pairs of subjects, one with and one without the outcome, in which the patient having the outcome had the higher predicted probability of having the outcome. The c index is equivalent to the area under an ROC curve, which is a reflection of the overall ability of the model to differentiate subjects with and without the outcome of interest. A c index of 0.5 indicates no predictive discrimination and a value of 1 indicates perfect separation of subjects with different outcomes.[104] The discriminative performance of alternative versions of the model, generated by eliminating various predictors, will be compared. The most parsimonious model(s) that has nearly as much discriminant ability as the full model will be adopted. ROC curves for the final

candidate model(s) will be plotted by varying the positivity criterion for predicted risk in the smallest increments that the data support from 0% to 100% and plotting the corresponding sensitivities and specificities. For each predicted risk positivity criterion we will also calculate positive and negative predictive values and likelihood ratios.

The calibration of the logistic regression model will be tested by calculating Brier scores.[105] The Brier score is the mean squared error of the probability predictions and ranges from 0 to 1. Zero indicates perfect calibration, one indicates complete mis-calibration, and up to 0.25 is considered chance agreement. For dichotomous events, the Brier score is given as $n\Sigma(y_k-o_k)^2$, where y_k is the predicted probability, and o_k is the observed outcome for each of the n forecast/event pairs. Calibration will also be measured using the Hosmer-Lemeshow goodness-of-fit statistic which uses chi-square tests after ordering observations by predicted probability, dividing them into equally sized groups and then calculating observed and expected probabilities in each group.[103] Because the Hosmer-Lemeshow test is sensitive to the number of groups compared, we will perform the test on different numbers of equally sized groups.

We will use a bootstrap technique to evaluate the possibility that the proposed model(s) is overfit and thus not generalizable to other patient samples. The bootstrap repeatedly chooses a new data set at random (with replacement) from the original data set and recalculates new regression coefficients. The "bootstrapped variance" of the regression coefficients over all the data sets is used with the original regression coefficients to compute new bootstrapped p-values. Coefficients that lose statistical significance in the bootstrapped p-value are likely the result of overfitting. Compared with other validation techniques, such as split sampling and cross-validation, bootstrapping provides nearly unbiased estimates of predictive accuracy that are of relatively low variance, requires fewer model fits, and uses the entire data set for model development.[36] If we find that the model is overfit, we will go back a step in the modeling process and redo the bootstrap on a one level simpler model.

Because the objective is to develop a practical prediction rules that clinicians can use in the clinical setting, we will develop a simple risk index using those predictors in the final model(s). To develop a risk index score for research purposes, one might use the regression coefficients for the individual risk factors as weights for calculating a score. However, a risk index that multiplies observed values by coefficients will not be practical. Therefore, we will explore the variables in the best model and assign each variable a transformed variable with values of 0,1 or 0,1,2, where 0 indicates a normal or non-problematic range, and 1 indicates abnormal; or 1 and 2 moderate and severe problems. We will sum up the values and explore the risk score cutoff that best separates the children who develop renal scarring from those who do not. In recognizing the importance of not missing cases, a cutoff value may be chosen that is somewhat conservatively low. This will create false positives, but decrease the false negatives. Depending on the variables in the final model, we may explore both transformations of a variable to 0,1 or 0,1,2 values. Further, although the multiple logistic regression modeling may give several competing models, the one that yields the more useful, simple discriminatory index will be the one chosen for implementation as a risk index. The risk index will be designed so that it approximates the predictive accuracy of the regression models from which it is derived. Using the same techniques discussed above, we will compare the discriminative ability and calibration of the regression model and its corresponding risk indices.

6.1.4 Analyses for the Secondary Aims - Recurrence of UTI and Predictive Model

The definition of recurrent UTI as a secondary endpoint is that it has to meet the exact same stringent criteria as the index UTI and its onset occurs more than 2 weeks from the last day of treatment for the preceding UTI, or following a negative urine culture. The analytic approach of (1) testing for equivalence of proportion of recurrent UTIs between patients who had VUR and were treated with placebo after their first or second UTI (RIVUR patients) and patients who did not have VUR after their first or second UTI (recruited as patients to this study) and (2) building a predictive model will be identical to the approach described above for the renal scarring outcome.

In comparing differences in recurrent UTI between the two groups we will adjust for known risk factors for recurrent UTI (such as age, gender, race, circumcision status) using multivariable logistic regression models (for recurrent UTI (yes/no)) and Cox Proportional Hazards models (for the time to recurrent UTI). We will also determine whether the 2 groups are different in terms of other factors not known to be associated with recurrent UTI, and we will adjust for those factors as well in order to control for any potential unrecognized confounders.

6.1.5 Safety Analysis

All subjects entered into the study at Visit 1 will be included in the safety analysis. The frequencies of AEs by type, body system, severity will be summarized. SAEs (if any) will be described in detail. This is an observational study and so we will report only AEs and SAEs directly related to the study and not to underlying illness. AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

6.2 Sample Size and Power

The sample size calculations provided below assume that we will combine data from approximately 150 children in RIVUR and 360 children in CUTIE (N=510). Although the RIVUR study is expected to begin enrollment in March 2007, and this study is planned to commence in Fall 2007, the accrual goals stated below are still expected to be accomplished, as described in Section V.B.3. In order to reduce confounding related to site-specific patient characteristics, we have restricted subjects for comparison to those from the 3 sites participating in both RIVUR and CUTIE, and therefore have chosen not to include all 300 anticipated placebo treated children in RIVUR. However, if there are no significant differences between RIVUR enrolled children from the 3 CUTIE sites and the other sites; we will consider increasing our sample of placebo-treated RIVUR children (and therefore our power) for all analyses. The sample size and power calculations provided below assume the more conservative and smaller anticipated sample. Because of the structure of this study as an ancillary study to the RIVUR study, the sample size is pre-defined. The calculations below show that the specific aims of this study are achievable with this sample size.

Table 6 lists sample sizes needed to test equivalence[106] in the proportion of children who have renal scarring on the outcome DMSA scan among:

Table 8. Sample size for equivalence testing

% of A and B with renal scarring on outcome DMSA scan	Sample size
0.10	79+190=269
0.13	100+238=338
0.15	112+269=380
0.20	141+337=477

1) Children in the CUTIE study who do not have VUR, and;
2) Children in the RIVUR study who do have VUR and are receiving placebo.

All comparisons assume α=0.05 (one-sided for equivalence – difference in proportions farther from zero in the same direction), power=80%, equivalence limit difference in proportions=0.10, expected difference in proportions=0 and ratio of numbers of children in A and B of 150:360 (150 in A and 360 in B) (Table8). The rate of renal scarring is assumed to be equal in groups A and B, and is estimated in the 10-15% range—in the lower range of previous reports but more consistent with a population with first UTI drawn largely from primary care practices as opposed to subspecialty clinics. Based on assumptions discussed above in the section on recruitment and consent, we anticipate a scarring rate of approximately 15% in the two groups, for which we will have more than adequate sample size (150+360=510) to reject the null hypothesis of lack of equivalence, assuming an attrition rate of 10% per year.

Table 9. Detectable ORs for risk factors

% of children without risk factor who have renal scarring	0.10	0.05	0.10
% of children who have the risk factor	0.30	0.30	0.20
Detectable OR for renal scarring in children who have the risk factor	**2.2**	**2.8**	**3.1**

The power calculation for development of a prediction rule involves (1) estimating the number of covariates that can be considered in the multivariable logistic regression model; (2) calculating the detectable ORs for risk factors given our sample size; and (3) calculating the 95% confidence intervals for the sensitivity and specificity estimates for the prediction rule. We expect that approximately 13% (n=66) of the 510 children in the combined population (A+B) will have renal scarring on the outcome DMSA scan. In developing a clinical prediction rule, a standard approach is that there should be 10 events in the study for every potential covariate included in the model. Using this guideline, we would be able to include up to 6 different covariates in a multivariate predictive model.

Table 10. Sensitivity and Specificity of Prediction Rule

A.1 Sensitivity	(N=66)
0.80	0.69-0.88
0.90	0.80-0.95
0.98	0.92-0.997
A.2 Specificity	**(N=444)**
0.40	0.36-0.45
0.50	0.45-0.55
0.60	0.55-0.64

95% Confidence Interval

Table 9 demonstrates that if 5-10% of children who do not have the risk factor develop renal scarring, and 20-30% of children have the risk factor, then our sample size will provide us with enough power to detect ORs for that risk factor in the 2-3 range (assumes total sample size=510, power=80% and alpha=0.05).

Table 10 shows the range of sensitivities and specificities and their respective confidence intervals based on the projected sample size. We expect robust estimates of the sensitivity and specificity given the narrow confidence intervals.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

7.3.1 Relationship of SAE to Study Drug or Other Intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated. As this study does not involve an investigational drug, we do not anticipate the need to characterize the relationship of SAEs to study drug.

7.4 IRB/IEC Notification of SAEs

The Principal Investigator will promptly notify the IRB of all study on-site SAEs and other unanticipated problems related to research using the CHOP Internal SAE reporting form and in accordance with the following timeline. External SAEs that are unexpected and related to the study intervention should be reported as they are received using the External SAE form (if applicable).

Table 11: Adverse Event Notification

Type of Internal Adverse Event	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 5 calendar days
Internal (on-site) SAEs All other SAEs	72 hours	Within 5 calendar days
Unanticipated Problems Related to Research	72 hours	Within 5 calendar days
All other AEs	N/A	Summary of AEs Reported at Time of Continuing Review

7.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. All SAE will be followed until either resolved or stable.

7.5 Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting will be consistent with the requirements of the IRB and the NIH.

7.6 Medical Emergencies

This is an observational study and so we do not anticipate medical emergencies. The site PIs will work with families to help get their children the care the require in the event of a medical emergency.

8 STUDY ADMINISTRATION

8.1 Data Collection and Management

8.1.1 Data Management System

A web-based data management system (DMS) will be used for this study. The data management system will provide all of the capabilities required for research data management, including: data transfer, data entry, data validation, database updating, database closure, data retrieval, data inventory, security and confidentiality, and archiving, and in addition will support randomization.

Each clinical site will be responsible for entering the data it collects. The clinical site staff will use the DMS to enter screening data and eligibility data, run an algorithm to determine eligibility, and for each eligible patient, the DMS will issue a random treatment assignment. Follow-up data will also be entered at the clinical sites into the DMS.

The server and main database reside at the DCC at the Collaborative Studies Coordinating Center (CSCC) at the University of North Carolina at Chapel Hill.

8.1.2 Data Entry, Editing and Reporting

Direct data entry, where data initially are entered on the screen without having completed a paper form first, will be available at each center. Direct data entry eliminates the time-consuming and error prone process of keying from paper forms. Paper versions of each data collection instrument will be available as backup in situations in which the computer systems are inaccessible for any reason. In addition, if there are forms that are routinely collected on paper for convenience or another reason, then the data on these forms will subsequently be keyed at the clinical sites using the web-based data entry system. The data entry system will display data entry screens that closely resemble the paper data collection forms. The system will be menu driven, with context-sensitive help available at any time. Each data field will be edited during entry.

The DMS will include the ability for each center to generate locally a variety of summary reports concerning the data completeness, outstanding questionable values, etc. This capability is valuable in permitting study coordinators to monitor the quality of their center's performance. This facilitates timely identification and resolution of problems in data collection and processing.

8.1.3 Central Laboratory Data Management

Reporting will be consistent with the requirements of the IRB and the NIH.

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8.1.3 Central Laboratory Data Management

The central laboratories will prepare data files from their local data management systems in a standardized format and transfer these to the DCC on a regular schedule. Upon receipt at the DCC, these data files will be processed for incorporation into the study's consolidated database. Alternatively, central laboratories may enter data into the study's web-based data management system.

8.1.4 Data Security

The DMS will require entry of a valid user ID and password for use. Sensitive files will be encrypted. Regular back-ups that are stored apart from the DMS server and database will be required.

All data transferred to the DCC will be stored, processed and analyzed within the CSCC office suite or its secure back-up location. At the CSCC, all access to office space containing data is controlled through locked doors. Visitors are screened by CSCC staff and cannot move about without a CSCC escort. All office space is locked after working hours. Access to computer data is controlled by passwords released only to those CSCC personnel who use the files. In addition, critical data files are encrypted.

8.1.5 Data Reporting

On a monthly basis, the DCC will prepare a study data report that provides clinic-specific and overall summaries of patients screened and randomized by month. Timeliness and completeness of follow-up contacts will also be reported. In addition, the DCC will routinely generate reports for the clinical sites and laboratories concerning data quality (missing or overdue forms, outstanding data queries, etc.), and facilitate the timely review, correction and resolution of data quality issues at the clinical sites.

8.1.6 Study Communications and Monitoring

The DCC will maintain current contact information on the study web page for all study staff from the clinical sites, central laboratories, central reading centers or committees, and DCC. Methods of study communications will include e-mail, web-postings, telephone, fax, regular mail, and express delivery services.

8.1.7 Technical Support

The study sites will have a liaison at the DCC who can be called for an immediate answer to an operational or data management question or for help in obtaining clarification of a particular situation. For each site, a primary study coordinator is identified, and a principal pediatrician or urologist investigator is identified who has the overall responsibility for the recruitment of patients and management of the study at the center.

8.2 Regulatory and Ethical Considerations

8.2.1 Data and Safety Monitoring Plan

Because this is an observational study, we will not establish an independent Data and Safety Monitoring Board (DSMB) for this study. The site PIs will be charged with approving and/or making recommendations to the final draft of the protocol, as well as monitoring recruitment and retention and reviewing data for safety. Table 12 details the frequency and

types of reports.

Table 12. Frequency and types of reports

Type of Report	Prepared By:	Provided To:	Frequency:
Serious Adverse Events (SAEs)	PI	DSMB/EAP, IRB	Immediately
Patient Recruitment/Targets	BDMC*	PI	q month
Data Quality, Timeliness	BDMC	PI, DSMB	q 6 mos
Demographics (combined)	BDMC	PI, DSMB	q 6 mos
Adverse Events (combined)	BDMC	PI, DSMB	q 6 mos
Final analysis	BDMC	PI, DSMB	After completion of follow-up

*Biostatistics and Data Management Core under Dr. Cnaan's guidance

8.2.2 Risk Assessment

8.2.2a Risk of Recurrent UTI and Renal Scarring

There is a risk that the children in CUTIE will develop recurrent UTI and renal scarring.

8.2.2b Pain and Discomfort of VCUG and DMSA scan

Although VCUGs and DMSA scans are routinely performed in the evaluation and monitoring of children with UTIs, they can cause pain and discomfort. DMSA scans require placement of a peripheral IV catheter and infusion of a radioisotope. IV placement can be painful for children and IVs can be dislodged and result in infusion into soft tissue (infiltrates). VCUGs require urethral catheterization and filling of the bladder with contrast material, both of which can be uncomfortable to children.

8.2.2c Radiation Exposure

Both VCUG and DMSA scan are sources of radiation. The radiation exposure for each of the scans is summarized below in Table 13, along with the dose for natural radiation exposure as a reference. The International Commission on Radiological Protection (ICRP) recommends calculating the effective dose equivalent (EDE) for each procedure. This measure incorporates weighting factors for the radiosensitivity of the different body tissues.

Table 13. Comparative Effective Dose Equivalents

Source	Effective Dose Equivalent (mrem)
Natural Radiation Sources	
Natural background radiation at sea level	300 per year
Roundtrip transcontinental airplane flight	6
Routine X-Rays	
Lateral lumbar spine chest x-ray	70
PA chest x-ray	5
Dental x-ray	10
VCUG	79-190
Tc-99m DMSA	69-155

The total EDE is the weighted sum of the effective does to all organs irradiated by the scan. The proposed study will not expose subjects to more radiation than under current practice, except to the degree that the protocol requires follow-up studies not usually performed.

8.2.2d Blood Draws

Blood draws may cause mild pain, bleeding, or bruising. Fainting and infection are rare complications.

8.2.2e Loss of Confidentiality

There is a risk of loss of confidentiality.

8.2.3 Potential Benefits of Trial Participation

Participants in the study potentially will benefit from earlier detection of UTI and renal scarring. The risks to subjects are reasonable in relation to the anticipated benefits. All of the evaluations and measurements performed in this study are considered within the realm of standard care for children with UTIs. Understanding the risk factors for renal scarring and recurrent UTI in both children who do and do not have VUR has the potential to identify children who might benefit from medical or surgical intervention, while sparing low risk children potentially harmful diagnostic evaluations and interventions.

8.2.4 Risk-Benefit Assessment

8.2.4a Risk of Recurrent UTI and Renal Scarring

The protocol should minimize this risk by providing increased attention to early detection and treatment of UTIs, increased frequency of monitoring for renal scarring, and strict and conservative protocol exit rules. Children who meet criteria for treatment failure outlined in the parent RIVUR study will have an early outcome DMSA performed and will be referred to a urologist for further management.

8.2.4b Pain and Discomfort of VCUG and DMSA Scan

All the procedures and exams will be performed according to strict standards by healthcare providers expert in the care of children and, if necessary, with the assistance of child life specialists, thus minimizing the risk of physical or psychological harm.

8.2.4c Radiation Exposure and Quality Control

VCUG procedures are conducted and supervised by qualified radiologists and X-ray equipment is frequently evaluated by qualified medical physicists and technologists. All three study sites have effective and prompt in-house biomedical engineering service and manufacture contract services to maintain performance of the X-ray equipment. All DMSA scans are conducted under the supervision of an authorized Nuclear Medicine physician. Dose calibration equipment and Gamma cameras are calibrated frequently by qualified individuals.

8.2.4d Blood Draws

Blood draws will be performed by qualified nurses, physicians and phlebotomists according to standard phlebotomy techniques.

8.2.4e Potential Loss of Confidentiality

To ensure subject confidentiality and comply with HIPAA regulations, no personal information, such as names, contact information, social security numbers, etc. will be stored in the DCC database. Electronic tables linking study ID numbers and personal information will be password protected and stored on site PI's password protected computers. Physical files linking study ID numbers to personal information will reside in locked limited access files in PI offices.

8.2.4f Abnormal Test Results

Copies of all radiology study result reports will be sent to the site PIs, the subject's parents/guardians, and the primary care provider. Subjects who meet treatment failure criteria established by the parent RIVUR study steering committee will have early outcome DMSA scans and will be referred for evaluation by the Urology Department at each site.

8.2.4g Monitoring of Adverse Events

Adverse events will be monitored by either the Data and Safety Monitoring Board (DSMB) empanelled for the RIVUR trial or by an independent External Advisory Panel assembled specifically for this ancillary study. (see section 8.2.1 Data and Safety Monitoring Plan above).

8.3 Recruitment Strategy

8.3.1 Background to Recruitment Strategy

The AAP recommends that all children with an initial UTI have a renal ultrasound to rule out anatomic abnormalities of the kidneys and urinary tract, and a voiding cystourethrogram (VCUG) to evaluate for presence of VUR, a presumed risk factor for renal scarring.[13] Several studies have demonstrated that many children with UTI do not receive these recommended tests. In a recent study of all children enrolled in Washington state Medicaid who had a UTI episode in their first year of life, only 40% received a VCUG and 44% received a renal US.[107] In a similar study of children enrolled in Alabama Medicaid, only 44% of patients younger than 8 years of age received both a VCUG and renal US after a UTI, and in a subset of patients with multiple UTI episodes only 68% had imaging studies.[108] The poor adherence to AAP recommended imaging guidelines is not limited to children enrolled in Medicaid. Among all children with an initial UTI in the first 2 years of life seen at the Kids First Practices and Primary Care Centers at CHOP in the last 5 years, only 63% had a VCUG performed. Among children ages 2-6, the proportion that had a VCUG after a first UTI episode was even lower (30%). In order to improve the quality of care for CHOP patients after a first or second UTI, staff members of the study team will work with willing providers to schedule renal US and VCUGs in an effort to increase adherence to AAP recommendations on imaging for these children.

8.3.2 KIDS First and Primary Care Practices

In order to facilitate scheduling of recommended studies for children with UTI, a Best-Practice Alert pop-up window informing providers about the scheduling option will appear in the Epic Electronic Health Record when the provider opens up a positive urine culture result

to report to a family. The provider will then choose whether to offer the family the research team's services in scheduling the renal US and VCUG. If the provider offers the option and the patient agrees, the provider will use the Smartset to send a message within Epic to the research coordinator that the patient requires scheduling of a renal US and VCUG. Within 24 hours the research assistant will telephone the family of the patient and the radiology department to schedule the studies at a time that is suitable for the family. After the research assistant schedules the studies, he/she will generate a telephone encounter within Epic to the referring provider confirming that the studies were scheduled. The studies will be scheduled listing the referring provider as the primary doctor so that the study results will be routed to him/her. The research team will send a reminder notice by mail to the family informing them of the date and time of the study, along with directions to the imaging center (either CHOP Main or King of Prussia) and information about the imaging studies to be performed. Within 2 business days following the child's imaging study, the research team will access the child's Epic account and determine whether the child had the studies performed. The research team will then notify the primary care provider through an EPIC telephone encounter about the status of the studies (completed or not completed).

If the patient completed the VCUG, the provider can then ask the family if they are willing to be contacted about one of two research studies. If the patient has grades I-IV VUR, the provider can obtain permission for the research team to contact the family about the RIVUR research study (CHOP IRB protocol # 2006-9-4957). If the patient does not have VUR, the provider can obtain permission for the research team to contact the family about the study. If the family provides verbal consent to the provider to be contacted about one of the two studies, the provider will notify the research team using the Smartset by sending a message within EPIC. If the family does not consent to be contacted, no further contact will be made by the research team to the family.

If the CHOP provider or family chooses not to use the research team's scheduling services, but the patient still has a VCUG performed, the provider can still ask the family if they would be intereseted in being contacted by the research team about one of two research studies. If the family provides verbal consent to the provider to be contacted about one of the two studies, the provider will notify the research team using the Smartset by sending a message within EPIC. If the family does not consent to be contacted about one of the two studies, no contact will be made by the research team to the family.

In addition to this passive approach of relying on providers to use the Best Practice Alert in Epic, study team members will send a telephone encounter reminder to those providers who have a potentially eligible patient but don't use the Best Practice Alert. This reminder will tell them about the study and that we are available to help schedule a VCUG and ultrasound for their patient. This would involve looking at the list of patients that the automated system identifies with new UTI, entering the patients' electronic health record, and sending the telephone encounter reminder to the provider.

All communication with providers and parents around the child's imaging needs will be performed separate from recruitment for the two research studies. These communications will be performed as part of a quality improvement effort and the research team members participating in the effort will be temporary members of the care team during the scheduling process. Communication with providers will occur within the Epic EHR (rather than e-mail) to preserve patient confidentiality and to facilitate documentation of plans around scheduling of the child's imaging studies. Access to the child's medical records by the research team will be limited to viewing contact information, administrative records of visits

for imaging, and imaging result to determine eligibility During the months of August and September of 2006, Drs. Keren and Canning met with the directors of the Practice Based Research Network and providers from 21 Kids First and Primary Care practices to discuss the study and scheduling service. Their responses were overwhelmingly positive and supportive of the approach outlined in this document.

8.3.3 CHOP Urology Department and Subspecialty Care Clinics

The Study Coordinator will scan the daily schedules of the CHOP main urology department and subspecialty care clinics within EPIC for potentially eligible patients. If a patient appears to be coming in for a urinary tract infection, the research assistant will attempt to confirm that the patient has not had any previous VCUGs performed or prior positive urine cultures by consulting the patient's urology chart and laboratory and imaging data. If the patient appears eligible, the research assistant will send an email to the urology attending physician seeing the patient the day prior to the appointment notifying them that the patient may be eligible for one of the two research studies.

In addition, an eligibility sheet detailing the study eligibility criteria will be placed in the patient's chart prior to the appointment to remind the urology physicians that the patient may be eligible for the study. The research assistant will send an email to the chart personnel in the urology department instructing them to include this sheet in the patient's chart when it is prepared for the appointment.

Upon seeing the patient, the urology physicians will determine if the patient is eligible for the study and the family is interested in being contacted by the study team. If the patient is eligible and the family is interested, the physician will complete the eligibility sheet with the family's contact information and forward it to the research team. If the family is not eligible and interested, the research team will not contact the family about the studies. The physician will indicate that the family is not interested or the patient is not eligible on the eligibility sheet and forward it to the research team so that we may track recruitment efforts.

8.3.4 CHOP Emergency Department

In the CHOP Emergency Department (ED), nurse practitioners have the responsibility of reviewing the urine culture logs from previous days to identify positive cultures, communicate results to patients and providers, and ensure that children receive appropriate antibiotics for positive cultures. The ED nurse practitioners will review the charts of patients with a positive urine culture and determine if the patient may be eligible for the "Careful Urinary Tract Infection Evaluation" study. The nurse practioner will send a fax sheet along with the urine culture results to the providers of patients seen in the CHOP ED that appear to be eligible. The fax sheet will notify the provider of the positive urine culture and the opportunity to have a VCUG and renal ultrasound scheduled by the research team. The fax sheet will also contain contact information to reach the research team for assistance in scheduling the imaging studies.

If the research team schedules a VCUG and/or renal ultrasound for a patient, the research team will ask the provider to ask the family if they would be willing to be contacted about the study. If the patient has Grades I-IV VUR they will be contacted about the RIVUR study and if the patient does not have VUR they will be contacted about the CUTIE study. Subsequent communications between the research team and providers who utilize the scheduling service will occur via Epic telephone encounters for providers within the CHOP

network and telephone, mail, or e-mail for providers outside of the network. The nurse practitioner will notify the research team about the patients to whom a fax sheet was sent to their primary care providers. Primary care providers not within the CHOP network will be sent informational packages about the appropriate study, including both provider and patient study brochures.

The ED nurse practitioner will also notify the research team of all children who were admitted from the ED to the hospital ward. The research assistant will speak with the providers caring for the patient on the ward, asking them to request the family's permission to be approached about the study. The research assistant will only approach families from the hospital ward after receiving such permission.

8.3.5 CHOP Radiology Department

Under the guidance of Dr. Richard Bellah, who is a CHOP radiologist and RIVUR co-investigator, and Tracy Monroe, the Marketing & Outreach Manager of the Department of Radiology, the clerks at the radiology registration desk will ask parents of children 2-72 months if they are having a first VCUG after a UTI. If so, the clerks will hand the parents a pre-assembled folder that contains the following recruitment materials (all included in the IRB submission):

1. Cover letter
2. CUTIE Study Brochure
3. Contact Information Form

During their visit for the VCUG, parents will have the opportunity to review the cover letter and CUTIE study brochure. The cover letter informs parents of research occurring at CHOP to elucidate best practices in the management of children with UTIs. It will inform the parents that if their child is found to not have VUR, he/she may be eligible to participate in this research. The CUTIE Study Brochure has been previously approved by the CHOP IRB. Parents whose children are found to not have VUR will have the choice of completing the Contact Information Form in order to have one of the Study personnel contact them by phone to tell them more about the CUTIE study. The radiology technologists who perform the VCUG (again under the supervision of Dr. Bellah) will ask families of children who do not have VUR if they had a chance to review the cover letter and CUTIE study brochure, and whether they elected to complete the Contact Information Form in order to be contacted about the study. The radiology technologists will collect completed Contact Information Forms and place them in a folder in the fluoroscopy work room. The folder will be stored in a locked file cabinet. CUTIE study coordinators will pick up completed forms from the fluoroscopy work room folder on a bi-weekly basis. The form will be handed to one of the CUTIE investigators (all MD's), who will contact the families to provide more information and answer any questions about the study. The forms will be kept in locked research file cabinets at 3535 Market Street.

8.3.6 CHOP General Pediatrics Inpatient Wards

Flyers detailing the CUTIE research study inclusion and exclusion criteria are posted in the inpatient General Pediatrics physician workrooms. If a patient is admitted for a urinary tract infection, the inpatient physician will notify the study team about the patient. If the patient has had a negative VCUG while in the hospital and meets basic eligibility criteria, the

inpatient team will get parental permission for the CUTIE study doctor and/or team to speak with the family about the RIVUR study. If the patient is not found to have VUR, or if the parents are not interested in speaking with the RIVUR team about the study, the RIVUR study doctor and/or team will not approach the family. If the patient is not having a VCUG performed while in the hospital, the inpatient physician can offer the scheduling service to the family to set up the child's VCUG and renal ultrasound.

Positive urine cultures within the inpatient units are monitored by Epic electronic health record staff. The Epic staff will send daily updates to the study team regarding positive urine cultures. If the study team receives a notification about a patient that has not yet been referred, the study team will contact the inpatient physician to discuss patient eligibility. If the patient is eligible, the study team may approach the family about the study as long as prior permission was obtained from the family by the inpatient physician.

8.4 Informed Consent/Assent

Families identified through the outpatient setting (Kids First and Primary Care Center Practices, Emergency Department, Radiology Department, Urology Practices) who agree to be contacted about the study will receive a phone call from a research assistant or the study coordinator. The procedure for requesting permission contact families about the research study will vary by study site as specified in the section above. On Monday through Friday, research coordinators and assistants at study sites will contact families who granted permission to be contacted in the previous days, explain the research study protocol, determine eligibility, answer all questions, and schedule an appointment within a week of UTI diagnosis. For children identified in the hospital, consent and baseline questionnaire and studies may be completed prior to discharge.

The research team will meet the family in the CHOP Urology Department or King of Prussia specialty care center for the baseline visit. A study doctor from the CHOP investigative team will discuss the study with the family, answer any questions that they have, have the parent(s) or guardian(s) sign the informed consent, determine final eligibility for the study,, begin the evaluation process and perform/schedule baseline studies.

The consent document, acquired from participants' parent(s) or legal guardian before the child is enrolled in the study, will describe potential risks and benefits of study participation as well as the responsibilities of the study participants, parents or legal guardians, and investigators, as well as give the parents/guardians an opportunity to consent or decline the collection and storage of DNA specimens. This consent document is written in language understandable to the adult providing consent as the child's responsible representative.

The National Commission for Protection of Human Subjects of Biomedical and Behavioral Research established age 7 as a reasonable minimum age for involving children in some kind of assent process. The children in the proposed study will be less than or equal to six years of age at the time of enrollment and so their cognitive abilities will be limited such that they cannot reasonably be consulted. Children who turn 7 while enrolled in the study will be asked to verbally assent to continued participation in the study. The proposed research protocol involves greater than minimal risk but presents the prospect of direct benefit to the individual subjects. For this reason we will require the consent of only one parent or legal guardian to enroll the child in the study (45 CFR §46.408), though we will attempt to obtain the consent of both parents or guardians, unless one is deceased, unknown, incompetent,

or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

8.5 Payment to Subjects/Families

Parents will receive discounted parking on-site and 2 meal vouchers for the CHOP Cafeteria (compliments of the CTRC) if the study visit is at the Main Hospital. Parents will also receive $50 for measurements completed at baseline and 24 months, and $25 for measurements completed at 6, 12, and 18 months for a total of $175 if all study visits are completed.

9 PUBLICATION

Publication authorship will be based on the relative scientific contributions of the investigators and key personnel. We do not anticipate the development of any intellectual property as part of this research study.

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Chapter 2: Recruitment, Screening, and Eligibility

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Chapter 2: Recruitment, Screening, and Eligibility

2.1 Overview

Recruitment and retention of an adequate number of study participants are critical to the success of any observational research study. To try and maximize the number of eligible participants enrolled into the CUTIE study, and to help enroll children from a broader spectrum of severity of illness, CUTIE clinical sites will be recruiting as either primary (acute) care sites, or subspecialty (referral) care sites. This chapter outlines the steps leading up to enrolling a participant into the CUTIE Study.

2.2 Recruitment

2.2.1 Recruitment Materials

Each participating clinical center will have developed its own preferred mechanism for recruiting participants, developing multiple strategies tailored to their catchment areas and the populations served. Brochures describing the CUTIE study will be the responsibility of each site to facilitate their recruitment.

Investigators should consider sending brief information letters or study brochures to all physicians in the catchment area, describing the goals and methods of the study. This should be done before the study starts, and periodically throughout the recruitment phase. Referring physicians should be supplied with materials that detail the study requirements for medical record documentation. It will be important to maintain a good relationship with referring physicians, keeping them informed of the study and their participants' progress. In addition, educational presentations to medical, nursing and other health professional groups should be scheduled to help with recruitment.

The role of the Study Coordinator is crucial. The most successful person for recruitment is an energetic and dedicated Study Coordinator who plays a central and multifaceted role. This individual is trained on all protocol details and is the local resource person for CUTIE physicians, referring physicians, participants and their families, the Data Coordinating Center and the NIH/National Institute of Diabetes and Digestive Kidney Disease. The Study Coordinator should show dedication, honesty, and deal sympathetically with potential participants and their families. Concern for the overall health and well-being of the study participants is their highest priority.

2.2.2 Recruitment Goals

The goal of recruitment is for each of the three clinical sites to recruit and enroll 120 patients over an 18-24 month period, for a total of 360 enrolled patients. Each site will recruit approximately 60 participants per year for the first two years. The recruitment at the sites is estimated to be 5 participants per month for 24 months.

2.2.3 Minority Recruitment

CUTIE clinical sites should strive to recruit all available minority participants that meet the eligibility criteria. Because minorities have generally been under-represented in previous research studies, they are less likely to be familiar with medical terminology, may not know anyone who has been in a 'good' research study, and may be suspicious of the medical system. Additional time may be required to educate potential participant families prior to the participant's enrollment. Sites may be required to enlist the services of an interpreter to facilitate recruitment in non-English speaking participants.

Study Coordinators and other personnel with whom the participants will have contact should be sensitive to different cultural and ethnic attitudes and practices. For example, personnel should be aware of days of special significance when scheduling follow-up visits; this may help improve participant compliance. Whenever possible, individuals from different minorities should be represented in the study staff.

2.3 Screening

2.3.1 Overview

In brief, the screening process will identify potential study participants who appear to meet the CUTIE eligibility criteria. The most critical screening factor for CUTIE recruitment is timing. In order to be considered for study inclusion, a child (aged 2 to <72 months) who has been recently diagnosed with their first or second urinary tract infection (UTI), no Vesicoureteral Reflux (VUR), and has documentation of fever or symptoms within ±24 hours of the beginning date of UTI work-up will need to have been appropriately treated and have been scheduled for a renal ultrasound and a voiding cystourethrogram (VCUG). An ultrasound and VCUG must be performed within 16 weeks of the date of the index UTI diagnosis. Another timing consideration is that enrollment must be carried out within 16 weeks of the index UTI diagnosis.

2.3.2 Screening Tools

A tool that will be helpful in screening is the Eligibility and Enrollment Form. This form may be used on paper to track a subject's eligibility, but ultimately, its main purpose is to verify eligibility and after deeming a child to be eligible, enroll him/her into the study. Do not begin data entry of this form during the screening process.

A log has been developed for those sites whose IRB requires tracking of potential participants. The Participant Screening Log (PSL) is a required form and will be entered into the CUTIE DMS. The data collected on the PSL will enable the sites to determine where their efforts in screening will be the most effective.

2.3.2.1 Documentation and Screening Timeline

The child is eligible for CUTIE if they have had 1 or 2 UTI's. In the event that more than one UTI has occurred, in order for the child to be eligible, he/she may not have been treated with prophylactic anti-microbials nor had a VUR diagnosis. The UTI immediately preceding the enrollment into CUTIE will be called the index UTI. The date of the index UTI diagnosis is defined as the collection date of the urine sample that resulted in the positive urine culture. In order to complete the screening within the enrollment time restriction (16 weeks since the index UTI diagnosis), the study staff will need to be able to determine that the index UTI meets the CUTIE–designated UTI definition (≥38°C fever OR symptoms occurring within 24 hours of medical care related to urinary tract, i.e. dysuria, urgency, frequency, abdominal pain, foul-smelling urine, and in infants, dehydration, hypothermia, and failure to thrive), was caused by a single primary organism, was appropriately treated, and that the child does not have vesicoureteral reflux (VUR). A list of exclusion criteria must also be reviewed, most of which may be determined from a child's medical history and ultrasound results.

The documents necessary for eligibility determination consist of the child's medical records from the index UTI visit, including medical history, documentation on fever, symptoms, urine specimen type, urinalysis results, urine culture results including anti-microbial sensitivity results, and local reports from the ultrasound and VCUG. Timely collection of supporting documentation and direct action regarding scheduling of radiographic procedures following a child's first UTI will increase the success of CUTIE recruitment. Source documents are required to document that the eligibility criteria have been verified.

The progression of events leading up to enrollment include early identification of a child who has recently been diagnosed with his/her first or second UTI, scheduling of radiographic procedures, documentation collection, eligibility determination, consent, and scheduling of the baseline visit.

2.4 Eligibility

2.4.1 Inclusion Criteria

2.4.1.1 Age of Participant

Date of birth is obtained to calculate age. At the time of enrollment, the patient must be older than 2 months of age, but less than 6 years of age (72 months). If the prescreening indicates that a patient is between 1 and 2 months of age, but will be at least 2 months when enrollment occurs, the Study Coordinator should continue to collect eligibility documentation for the child. If the prescreening indicates that the patient will be 6 years of age or greater at the time of enrollment, then the patient should not be screened any further.

If a child is less than 6 months of age, their gestational age must be greater than or equal to 34 weeks in order to be accepted into the study.

2.4.1.2 First or second Febrile or Symptomatic UTI

The child who is being considered for inclusion into CUTIE will need to have been diagnosed with either a febrile UTI or a symptomatic UTI ($_{F/S}$UTI) that fits the definition that follows. The UTI must meet one of the two criteria (febrile or symptoms) listed under section I AND meet one of the three pyuria criteria listed under section II AND meet one of the two

criteria for proof of infection listed in section III. This UTI definition remains constant for all CUTIE UTIs.

I. Fever[1]

- Documented temperature of at least 100.4 °F or 38°C, measured anywhere on the body either at home or at doctor's office

OR

Symptoms

- Suprapubic, abdominal, or flank pain or tenderness, or urinary urgency, frequency, or hesitancy, or dysuria, or foul smelling urine, or in infants ≤ 4 months old, failure to thrive, dehydration, or hypothermia

AND

II. Pyuria on urinalysis

- ≥10 WBC/mm^3 (uncentrifuged specimen) OR
- ≥5 WBC/hpf (centrifuged specimen), OR
- positive leukocyte esterase on dipstick

AND

III. Culture proven infection with a single organism[2]

- ≥5 x 10^4 CFU/mL (catheterized or suprapubic aspiration urine specimen) OR
- ≥10^5 CFU/mL (clean voided specimen).

2.4.1.3 Appropriately-Treated Index UTI

In order for a child to be considered eligible for CUTIE, there must be documentation that the index UTI was appropriately treated. Study Coordinator will need to acquire the urine culture results including anti-microbial sensitivity results for the index UTI. Treatment for the index UTI will be considered appropriate if antibiotic therapy continues for a minimum of 7 days and:

1) There is documented sensitivity of the organism to the antibiotic used for treatment OR
2) There is a documented test of cure (negative urine culture) 1-14 days after completion of therapy.

---

[1] Must occur within ± 24 hours of initiating workup for UTI.

[2] One contaminating organism may be present at colony count of ≤ 10,000 CFU/ml.

2.4.1.3 VCUG Radiographic Scan Results

Central to the CUTIE study is the absence of VUR. Timing of the VCUG is critical for entry into the CUTIE Study. The scan must be obtained and interpreted within 16 weeks of the index UTI diagnosis.

2.4.2 Exclusion Criteria

In addition to documenting that the child being screened meets all of the inclusion criteria for the trial, there is a list of exclusion criteria that will eliminate the child's eligibility if one or more criteria are met.

2.4.2.1 Renal Ultrasound Results

Many of the exclusion criteria may be documented from the renal ultrasound results. The renal ultrasound will be performed to screen for obstruction or other anatomic abnormalities of the urinary tract, such as urologic anomalies (hydronephrosis, ureterocele, urethral valve, solitary or profoundly small kidney, multicystic dysplastic kidney, pelvic kidney, or fused kidney).

The ultrasound scan must also have been obtained and interpreted within 16 weeks of the index UTI diagnosis.

2.4.2.2 Sulfa Allergy

If the child has any known allergy to sulfa medications or has G6PD deficiency or other conditions that are contraindications for the use of trimethoprim-sulfamethoxazole (TMP/SMZ), he/she will be excluded from the study. Further, if the child being screened has a parent or sibling with a known anaphylactic reaction to sulfa medications, he/she will be excluded from the CUTIE Study.

2.4.2.3 Other Medical Conditions

Any child who has any one of the conditions listed in Table 2.1 will be excluded from the study. There may be information in the child's medical records about these exclusion criteria, but the Study Coordinator may only have the parent's report as the supporting documentation. QxQs for the ERF will include specific definitions or other information necessary to make these assessments.

Table 2.1. CUTIE Exclusion Criteria

1. History of renal disease or injury
2. Bladder or renal surgery
3. Congenital or acquired immunodeficiency
4. Anomalies or chronic diseases that interfere with response to therapy such as chronic gastrointestinal conditions (i.e. malabsorption, inflammatory bowel disease)
5. Liver or kidney failure
6. Any malignancy
7. Any known syndromes associated with bladder dysfunction
    a. VATER - VACTERL association
    b. Townes-Brock syndrome (*SALL1* mutation)
    c. Cat eye syndrome (tetrasomy, chromosome 22)
    d. Casamassima - Morton-Nance syndrome
    e. Renal coloboma syndrome (*PAX2* mutations)
    f. Branchio-oto-renal syndrome (*EYE1* mutation)
    g. Frasier syndrome (*WT1* mutation)
8. Complex cardiac disease, defined as any cardiac anomaly where the child requires regular medication or where the child's cardiologist would prescribe perioperative antibiotics
9. Continued use of drugs that are contraindicated with sulfatrim (atropine, bezoic acid, hyoscyamine, methenamine, methylene blue, phenyl salicylate, benzocaine, butamben, tetracaine topical, dofetilide, lidocaine/prilocaine topical)

2.4.2.4 Inability to Complete the Trial

Another exclusion criterion for the CUTIE Study includes a family's inability to complete the study protocol. This includes whether or not the family has given consent for the child to participate in the study. Once consented and enrolled into the study, the child will be followed for a minimum of 2 years. If the family has any reason to move from the study area within 2 years following study enrollment, the child should be excluded. Hardships with regard to clinic transportation should be considered when discussing the family's ability to participate in the CUTIE Study.

2.4.2.5 Participating in Other Trials

Eligible participants who are currently participating in any other research study are welcome to participate in the CUTIE Study if the other study does not preclude the child from adhering to the CUTIE protocol in any way.

2.4.2.6 Pyuria or Evidence of UTI on Day of Enrollment

For a child to be eligible there cannot be pyuria or evidence of a UTI on the day of enrollment. To rule these out, the coordinator must ask the parent about any recent fever or symptoms and collect urine on the day of enrollment to dip for pyuria. This can be performed on a bag specimen. If the result is trace or higher, the coordinator should obtain a cathed specimen and dip again. If still positive, coordinator should order a stat microscopy from local lab on the cathed urine. A microscopy result of ≤10 WBC/mm3 (uncentrifuged

specimen) OR ≤5 WBC/hpf (centrifuged specimen) trumps the dipstick result and means the child is eligible. A positive microscopy result will require that the urine be cultured to rule out a UTI. In this situation, the coordinator should tentatively reschedule the enrollment visit and wait for the result of the urine culture.

If the culture results from the previous enrollment attempt show no bacteria, then the child may return to the clinic for enrollment. The coordinator should obtain a urine specimen and dip as usual during the second enrollment attempt. Even if the dip shows pyuria, the coordinator may continue with the enrollment if there has been no recent fever or UTI symptoms.

In rare situations a child may normally demonstrate positive pyuria. If the dip from the second enrollment attempt shows greater pyuria than the dip from the first attempt, the coordinator should be careful to rule out the possibility of UTI.

2.5 Consent

2.5.1 Participant Informed Consent

Informed consent is a legal condition whereby a person can be said to have given consent based upon an appreciation and understanding of the facts and implications of an action. The individual needs to be in possession of all of his faculties, such as not being mentally retarded or mentally ill and without an impairment of judgment at the time of consenting. Impairments include illness, intoxication, drunkenness, using drugs, insufficient sleep, and other health problems. In CUTIE, the parent(s) or guardian of the participant will be consenting for the child.

Informed consent is a process, not just a form. Information must be presented to enable persons to voluntarily decide whether or not their child will participate as a research subject. It is a fundamental mechanism to ensure respect for persons through provision of thoughtful consent for a voluntary act. The procedures used in obtaining informed consent should be designed to educate the subject population in terms that they can understand.

Included in the 'informed' process:

1. Description of the overall experience that will be encountered.
2. Description of the risks and benefits that subjects may reasonably expect to encounter.
3. The parents or legal guardian must be told the extent to which their personally identifiable private information will be held in confidence.
4. Identification of contact persons who would be knowledgeable to answer questions of subjects about the research, rights as a research subject, and research-related injuries.
5. Explanation of the right to withdraw at any time without penalty. It is equally important to explain any foreseeable consequences to them should they unilaterally withdraw while dependent on some intervention to maintain normal function.

Eligible children invited to participate in the CUTIE study will be consented for study enrollment. Each site's Project Coordinator or other trained study staff member must perform

the formal process of obtaining informed consent from the parent(s)/legal guardian of the child for enrollment. Failure to obtain informed consent and a signed consent form from the parent(s)/legal guardian of each potential participant before screening and/or before enrollment is a serious protocol violation. Note: Foster parents are not considered legal guardians.

The informed consent process must include an explanation of the nature of the study and its rationale, examination procedures, specimen and data collection procedures, enrollment, the duration of the study, the importance of compliance to study procedures, and the potential risks and benefits. Parents and/or guardians must be told that they are not obligated to participate, that there will be no penalty for declining to participate, and that their treatment will not be compromised if they choose not to participate or cease participation at any time.

Ample time must be provided for each parent or guardian to read and understand each site's IRB-approved consent form, and to ask questions. If a parent or guardian cannot read, clinic staff must read the consent form for the adult, or use an audiotape of the consent form. Parents or guardians who do not understand English should have the consent process administered in the participant's language in the presence of the Project Coordinator or appropriate recruitment staff, and the consent form must be translated in the language spoken by the patient and approved by the IRB at that clinical center.

2.5.1.1 Consent for Specimen Storage at the Repository

NIDDK/NIH has included in the CUTIE Study the opportunity for the participants to contribute to the NIDDK biosample and genetics repositories. Some of the specimens collected during the study will be stored at the central repositories to be used for future research. Each participant must be separately consented to contribute specimens to the NIH-designated repositories. These consents may be covered during the CUTIE consenting process. If a family has any desire to limit the specimens to be stored, they should be free to do so without repercussion. Each specimen collected has a 'date for use by' if the family does not wish for an open-ended time period of specimen retention.

2.5.1.2 Consent Tracking Form (ICT)

Each consented parent or guardian should receive a signed copy of the study consent. The site's signed consent form copy is to be filed with other confidential participant information. Upon completion of the consenting process, an Informed Consent Tracking (ICT) form is to be completed for each participant **prior** to enrollment. It is again completed on any contact occasion when the parent or guardian notifies the study that they would like to modify their consent, or withdraw from the study.

It is imperative that the Study Coordinator keeps track of what specimens have been consented for collection. It is a serious protocol violation to collect a specimen and ship it to a repository if the family has not consented. The report from the DMS will be able to keep the Coordinator informed, but the Coordinator will need to inform the phlebotomist about repository restrictions.

2.5.2 Obtaining a Medical Release

Endpoint data collection as well as adverse event reporting will require review and abstraction of medical records for health care received outside the clinical center's hospital. Study personnel must obtain a medical record release form to obtain data from the outside care provider. Medical release forms should include the purpose of the request, the information that will be requested, and the time period related to the request. The release form should be reviewed with the participant during the informed consent process, prior to the participant signing the form.

2.5.3 Health Insurance Portability and Accountability Act (HIPAA)

The Health Insurance Portability and Accountability Act (HIPAA) require that all research collecting identifiable health information on an individual be in compliance with HIPAA standards and regulations. HIPAA regulations specifically apply to research studies collecting Protected Health Information (PHI). PHI is defined by HIPAA as health information transmitted or maintained in any form or medium that:

1) Identifies or could be used to identify an individual; and
2) Is created or received by a healthcare provider, health plan or employer, and
3) Relates to past, present or future physical or mental health or condition of an individual.

Compliance for each Center will require that each participant read and sign a "HIPAA Authorization to Use and Disclose Individual Health Information for Research Purposes" form. These forms must receive IRB approval at the clinical site prior to their use and thus, prior to the enrollment of any CUTIE participant. The participant should receive a copy of her signed authorization.

In addition, all study personnel who have contact with potential participants or data are required to complete a course on human subjects' protection. Each Center PI and the directors of the Coordinating Center and Central Laboratories are responsible for ensuring that their personnel have completed an approved training program.

2.6 Scheduling an Enrollment Visit

Once a child is determined to be eligible for participation in CUTIE, and appropriate data is collected, the baseline visit should be scheduled for the child's enrollment. Informed consent can occur at this time, or at the beginning of the enrollment visit.

Chapter 3: Radiology

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Chapter 3: Radiology

3.1 Overview

Renal/bladder sonograms will be used to screen participants for obstruction or other anatomic abnormalities of the urinary tract. DMSA renal scans will be used to determine the presence and/or worsening of cortical defects, and to assess the severity of renal damage. Contrast VCUGs will be used to ensure patients do not have VUR. Results of all images will initially be interpreted at participating institutions. CUTIE study evaluations will be made through independent readings by reference radiologists and nuclear medicine investigators using standardized grading systems. These reference radiologists will make up the Imaging Studies Reading and Classification Committee.

3.2 Radiographic Images

3.2.1 DMSA

DMSA scans will be used to determine the presence of cortical defects. Renal images should be obtained 1 ½ - 3 hours after IV administration of an age-appropriate dose of DMSA. Administered dose of 3-5 mCi/1.73 m2 body surface area or 50-100 μCi/kg body weight (minimum dose of 0.5 to 1 mCi) is advised. Planar images obtained with parallel-hole collimator, with or without pinhole magnification, are acceptable. SPECT images are not acceptable for this study.

Planar Imaging without pinhole magnification:
Posterior and both posterior-oblique renal images should be obtained using a high-resolution collimator, 256 x 256 matrix, and 500,000 - 1,000,000 counts per image. Appropriate zoom should be used to eliminate bladder activity from the field of view. Differential renal function should be calculated on the posterior image by background subtracted number of counts in each kidney as percentage of total number of counts in both kidneys.

Pinhole Imaging:
A posterior image of the kidneys using a parallel-hole collimator (300,000-500,000 counts) should be obtained for calculation of the renal differential function. Magnified posterior and posterior-oblique images of each kidney are then obtained using a pinhole collimator with a 4 mm insert. 120,000-150,000 counts should be accumulated for each pinhole image.

Interpretation of DMSA scans:
Cortical defects (dysfunction) will be defined as focal or diffuse decreased uptake with or without volume loss. Using criteria established by Majd (1) defects with preserved contour (without volume loss) will be classified as acute pyelonephritis and those with obvious volume loss/cortical thinning will be classified as cortical scar. The cortical defects will be assessed semi-quantitavely by dividing the renal cortex into 12 equal segments. The location and number of renal parenchymal segments affected will be determined and the extent of the renal abnormality will be graded as outlined in Figure 1.

These evaluations will be made by two reference nuclear medicine investigators on the Imaging Studies Reading and Classification Committee.

See Appendix 1 for an example of a DMSA image.

Figure 1. Grading system for characterizing extent of renal scarring

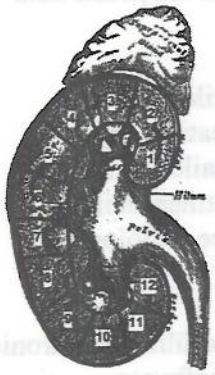


Figure 7. Grading system for characterizing extent of renal scarring

Grade	Description
1	1-2 kidney segments affected
2	3-4 kidney segments affected
3	>4 kidney segments affected
4	Global atrophy characterized by a diffusely scarred and shrunken kidney.

3.2.2 VCUG

A contrast VCUG will be used to ensure patients do not have VUR. Morphological abnormalities of the bladder and the appearance of the urethra will be noted.

Sedation during performance of VCUG is neither expected nor required as part of this trial. Institutional policies on sedation will not be modified for study participants. However, the study will record whether or not sedation is used and, if used, the name of the medication(s).

Results of the VCUG will be initially interpreted at participating institutions; the digital image will be acquired by two reference radiologist investigators on the Imaging Studies Reading and Classification Committee.

3.2.3 Renal/Bladder Sonogram (Ultrasound)

Renal/bladder sonograms will screen for obstruction or other anatomic abnormalities of the urinary tract, such as ureteropelvic junction obstruction, a posterior urethral valve, or hydronephrosis associated with an ectopic ureter or ureterocele.

3.2.4 References

1. Majd, M, Seminars in Nuclear Medicine 1992. 22: 98-111.

2. Rushton, H.G., et al., *Evaluation of 99mtechnetium-dimercapto-succinic acid renal scans in experimental acute pyelonephritis in piglets.* J Urol, 1988. **140**(5 Pt 2): p. 1169-74.

3. Andrich, M.P. and M. Majd, *Diagnostic imaging in the evaluation of the first urinary tract infection in infants and young children.* Pediatrics, 1992. **90**(3): p. 436-41.

4. Goldraich, N.P., O.L. Ramos, and I.H. Goldraich, *Urography versus DMSA scan in children with vesicoureteric reflux.* Pediatr Nephrol, 1989. 3(1): p. 1-5.

3.3 Clinical Site Procedures

3.3.1 Obtaining Scans

Coordinators should schedule and/or obtain radiographic images on participants as required per protocol and described in the MOP Chapters on baseline, follow-up, and endpoints data collection.

Non-protocol interim DMSA scans, requested by the DCC following a febrile UTI or treatment failure determination, are to be scheduled within 7 days of notification. Since assessment of these images is time-critical, images must be obtained and mailed to the reference radiologists as soon as possible. The DCC will notify sites of treatment failure determinations within 2 weeks after the images are received by the reference radiologists. Sites are asked to notify parents of any change in status within 3-4 days.

The images can be obtained either as electronic images on CD (preferred) or films. Electronic images should be collected as DICOM format with the site's local reading software. Coordinators will need to obtain three copies of all digital images, as well as associated local radiology reports. One copy is stored at the clinical site as study source documentation. The other two copies are sent to each pair of the reference radiologists (see Section 3.3.4).

3.3.2 Identification / De-identification and Encryption

No identifying patient information is included as study data, or entered into the study database for this pilot. Images, films, and reports are to be de-identified of patient information as required at each individual site prior to shipment to the reference radiologists.

If you are unable to de-identify the data sufficiently then you may use Winzip Pro 11.2 to encrypt the files before you send them to the reference radiologists. Please see Appendix 3.3 for more information on how to do this.

3.3.2.1 ID Labels

The DCC will provide pre-printed ID labels for each site. The ID labels correspond to the participant ID numbers, and include contact occasion and sequence number pre-filled for baseline, 12-month (CO=07) and end-of-study 24-month (CO=13) scans. Additional labels are included for non-protocol interim DMSA's. These will require recording of contact occasion and sequence numbers as appropriate. These radiographic labels will be used to identify the radiographic scans and allow us to identify studies that belong to a single patient.

The preprinted labels with participant ID numbers are to be affixed to CD cases, on every page of film, the local report pages, and the inventory and shipping logs. ID numbers including contact occasion and sequence number (see Section 5.2) also need to be written on the CD, marking on the top of the CD with a black sharpie.

3.3.3 Data Collection Forms at the Clinical Sites

- DMSA Sedation Form (DSF)
- DMSA Scan Shipping Form (DSS)
- VCUG Sedation Form (VSF)
- VCUG/US Scan Shipping Form (VUS).

3.3.3.1 Sedation Forms

A sedation form is to be completed for each DMSA and VCUG image, using the VCUG Sedation Form (VSF) or DMSA Sedation form (DSF) to document sedation used during the scanning. These forms are to be completed for each participant and scan, regardless of whether sedation was used. This is information the Coordinators must request at the time they are requesting the scans.

3.3.3.2 Shipping and Inventory Logs

When preparing to mail images to the reference radiologists you will need to complete the DMSA Scan Shipping Form (DSS) and/or the VCUG/US Shipping Form (VUS), providing and inventory of the collection and including the shipping date that correspond to the images being mailed. Each scan being shipped must be accompanied by an appropriate study shipping log.

Date from these shipping and inventory logs must be entered into the study DMS. Copies of completed logs associated with a shipment are to be included with each mailing. Coordinators can complete the accompanying logs by hand, or print off the data screen from the DMS.

3.3.4 Mailing Instructions

DMSA Images and corresponding local reports are to be mailed to:

Massoud Majd, MD
mmajd@cnmc.org
Children's National Medical Center
Department of Radiology
111 Michigan Ave., NW
Washington, DC 20010-2970
Phone: 202-884-5088

and

Harvey A. Ziessman, MD
hziessm1@jhmi.edu
Professor of Radiology
Director of Nuclear Medicine Imaging
Johns Hopkins Outpatient Center
601 North Caroline Street, Suite 3231
Baltimore, MD 21278

Phone: 410-955-5152
Fax: 443-287-2993

Ultrasounds Images and corresponding local reports are to be mailed to:

J Michael Zerin, MD
jzerin@dmc.org
5021 Champlain Circle
West Bloomfield, MI 48323
Phone: 248-538-9260 (home)
313-745-7080 (work)
Fax: 313-993-0393

and

Kassa Darge, MD, PhD
Professor of Radiology
Chief, Division of Body Imaging
Department of Radiology
The Children's Hospital of Philadelphia [CHOP]
University of Pennsylvania
324 South 34th Street
Philadelphia, PA 19104
Phone: 267-425-7133 [assistant]
267-425-7108 [direct]
215-283-3676 [pager]
Fax: 267-425-57155
Email: darge@email.chop.edu

When mailing scans, please send an email notification to each radiologist and the DCC using the preprogrammed email group available on the CUTIE Website for "DMSA Reference Radiologists" or "VCUG/US Reference Radiologists." The email should be titled 'CUTIE Radiology Shipment' and indicate the number of studies included, the date shipped, and the site sending the shipment.

There are no specific requirements regarding how to mail (i.e. US mail, FedEx) baseline scans; sites can choose the system convenient for them. Interim DMSA scans that indicate scarring on the local report will require a more time urgent procedure for shipping, analysis and reporting. These need to be collected as soon as possible and mailed FedEx overnight.

3.4 Radiologist Procedures

3.4.1 Storage and Extraction of Images/Films

If the files arrive from the site in an encrypted zip file format on CD then unzip the file to enable reading. To unzip the files please see instructions outlined in Appendix 3.4.

If files are downloaded from CD's to the radiologist's computer, folders must be created and named to match the ID label on the CD, indicating the ID number, contact occasion and

sequence number (i.e. MA02062_01_00). If possible, files on the CD should also be renamed when saved on the computer/laptop in the folders. **It is critical that there is a link from the images on the computer to the Participant ID number.**

All laptops and computers containing study data should be stored in a secured location.

3.4.2 Reading and Recording Scans

Each member within a pair of reference radiologists will read and record reading results independently onto separate forms in the Web based data management system (DMS). Images are to be read within 10 days of receipt. Interim images following a febrile UTI or treatment failure determination are time critical and must be assessed as soon as possible, within 7 working days.

Reading results can be recorded either on the paper data collection forms then entered, or entered directly into the DMS. At any time when reading results are recorded on paper prior to entry in the DMS, the paper is considered source documentation and must be saved for at least 2 years following the termination of the study.

3.4.3 Data Collection Forms needed by the Radiologists

Each image type has a data collection form associated with it, copies are included with the MOP and are also available on the study website.

- DMSA Results Form (DMF)
- VCUG Results Form (VRF)
- Ultrasound Results Form (URF)

3.4.4 Adjudication

Paired readings of images with any discrepant data items will require adjudication. The Data Management System (DMS) will have reports available that will identify images and reading results that need adjudication. These reports will be available to both members of the pair of radiologists. Section 3.5.5 will be added to this chapter at a later date and will contain a description of the DMS reports regarding radiology.

Adjudication of images is done by telephone conference, set up by the lead adjudicator. The DCC may occasionally sit in on the adjudication calls monitoring the process.

One member within each pair of reference radiologists will take a lead in managing the adjudication procedure, assuring the database reflects the adjudicated results. The lead adjudicator is responsible for setting up the communication for any needed adjudications twice monthly, and for the final data entry of the adjudicated results into the newly created adjudicated record (see Section 3.5.4).

The lead adjudicator is also responsible for keeping documentation on the decision making processes used in adjudicating results and on the comparing of notes taken during the individual readings. This documentation will be shared with the DCC and used to modify the

forms or procedures used in the main study and provide the appropriate documentation on the decision making of this study endpoint.

The assignment of the lead adjudicator can be alternated/shared among the pairs of radiologists, throughout the study. Notification to the DCC is required when making a change in assignment so that privileges to the DMS adjudication functions can be transferred.

3.5 Data Management for Reference Radiologists

3.5.1 Identification of Images

The clinical sites are responsible for labeling all images with the participant ID, contact occasion, and sequence numbers. These 3 numbers assure each image is uniquely identified. All participants will have DMSA's at baseline and 24-months, VCUGs at baseline and ultrasounds at baseline.

Contact Occasion numbers are as follows:

Contact Occasion	Visit
01	Baseline
13	24-Month Follow-Up

Participants who are deemed treatment failures may require DMSA scans at other times during follow-up in the study. These will be labeled appropriately by the clinical site with the correct contact occasion and sequence number.

The information that identifies each data collection form and/or each data record as a unique record in the CUTIE DMS is the key field information contained in the "header" box at the top of the first page on all forms.

ID Number – This is the first part of the ID label on each image received from the clinical centers, which corresponds to the participant ID. All CUTIE ID's are 7 fields long and include a site mnemonic as the first 2 fields, followed by 5 numbers that include a check digit for quality control.

Form Code / Version – identifies a unique data collection form. The results from reading the radiographic images are recorded on 3 data collection forms, one for each scan type. Versions will change as revisions are made to the data collection forms.

Contact Occasion and Seq# - These are the 2nd and 3rd numbers after the ID that is contained on the ID label of each image. For example: PT01515_01_00, the participant ID is PT01515, contact occasion 01 (baseline), and seq# 01 (the first occurrence within the ID and CO.

Each image reading is entered into 2 different files, one for each member of the radiologist pair. For data entry, the reference radiologists are assigned the following codes, which identify the form code for entry, providing unique records for each reading:

DM1 – Massoud Majd
DM2 – Harvey Ziessman
VR1 and UR1 – Michael Zerin
VR2 and UR2 – Kassa Darge

In the event that adjudication between the paired readings is necessary, a 3rd file is created that will have form codes DM3, VR3, and UR3. Only the lead adjudicator (Majd and Zerin) can modify data in the 3rd form. See Section 3.5.4 for specific instructions on how the adjudication process works in the DMS.

Administrative Information
The last set of questions on each CUTIE data collection form contains administrative information. This includes the date of data collection (image reading), the method of data collection (by paper recording first or directly into DMS), and the initials of the Radiologist. Entering the last field, initials of the radiologist into the DMS is the flag to the DMS and DCC that the image reading is complete and reports can be run. Until this section is entered, it is assumed that readings of this scan are not complete.

3.5.2 Official Study Documents

All current versions of the study MOP and data collection forms are available from the DCC.

3.5.3 Data Management System User's Guide

The CUTIE Data Management User's Guide is located in Chapter 14 of the CUTIE MOP. All DMS users should be familiar with this document.

3.5.4 DMS Query Resolution - Adjudication

Adjudication is a function performed under "Query Resolution." Only the lead adjudicator has write access to the adjudicated records, while the other radiologist has browsing privileges.

Once in the "Query Resolution" screen, the left hand panel will indicate the ID numbers of any images requiring adjudication of at least one data item. Clicking on the ID will identify the contact occasion and adjudication forms associated with the image.

Clicking on a file, will bring up an adjudication record (DM3, VR3, or UR3), which will be pre-filled with the values entered originally by the lead adjudicator. Fields that are in agreement will appear with shading and will not allow modification. Fields requiring adjudication will be blank. When the cursor is on each of these fields, pressing F1 will cause a comment to pop on the screen that provides the previous data values from both radiologists that are in need of adjudication.

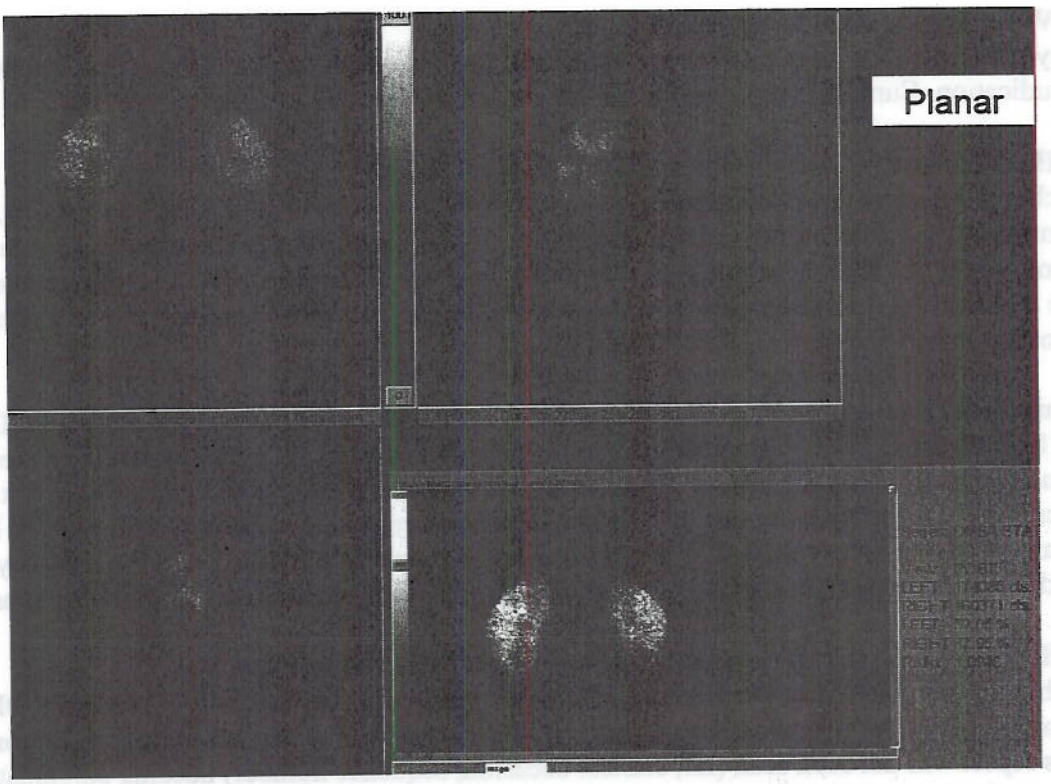
In the event that the adjudication process results in needing to change values on other fields that were not discrepant, that modification must be made through the normal "Remote Data Entry" process on the adjudicated file (DM3, VR3, or UR3), after resolution is complete. Changes needed on images reviewed that did not require adjudication are done in the original

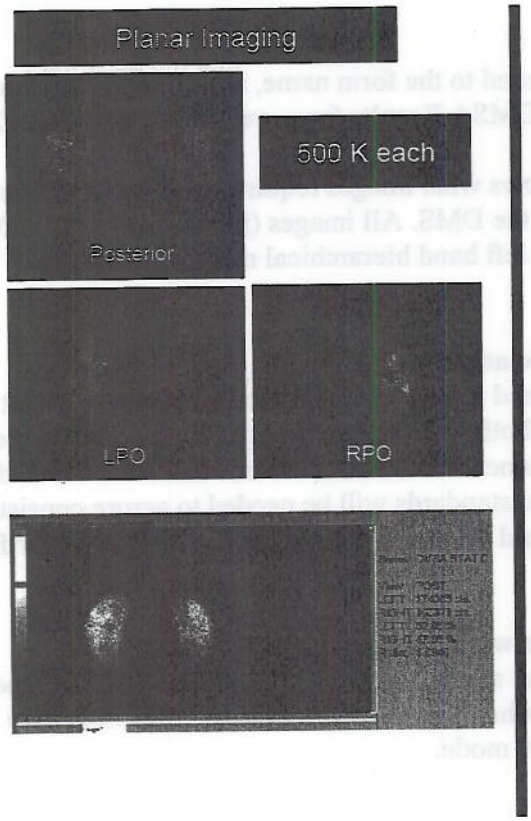
DM1-2, VU1-2, and UR1-3 files, which could result in adjudication if there are any new discrepancies.

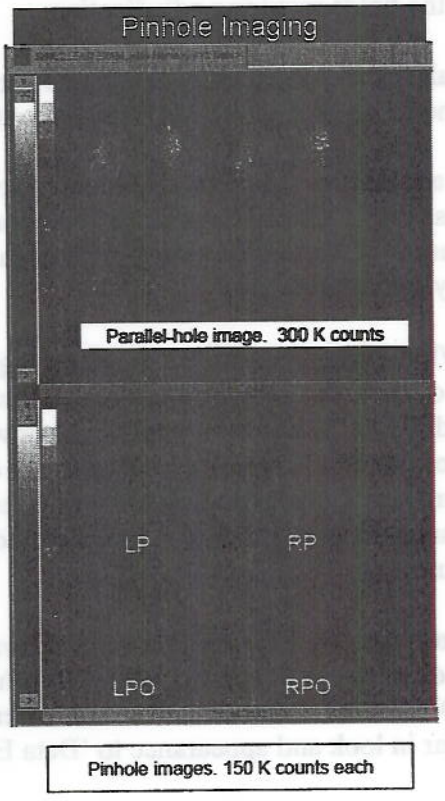
The DMS will have reports that will list out images and data items needing adjudication for both radiologists review.

Appendix 3.2 contains an FAQ providing more information on the adjudication process in the DMS.

Appendix 3.1 – Example DMSA Images







Pinhole images. 150 K counts each

Appendix 3.2 – CUTIE Image Adjudication FAQ

1) What images need to be adjudicated?
Any image result with one or more discrepant values between the 2 radiologists is flagged for adjudication. Currently, the adjudication system looks for a 1:1 exact match.

2) How are images determined to require adjudication?
Each night a process runs that looks for completed and matched records (matched on ID, Contact Occasion (CO), sequence number (Seqno), and form version), compares all data items, and assesses if there is the need to adjudicate any of the results. A completed record is one that has had the radiologists initials entered into the last administrative field of the image records.

If an adjudication is determined to be needed, the original records are locked (DM1, DM2, VR1, VR2, UR1, UR2) from additional entry or modification, and a new record is created for adjudication (DM3, VR3, UR3). The adjudicated record is pre-filled with data that is not discrepant. These fields are also greyed out. The fields requiring adjudication have been left blank and are easily identified. With the cursor on a blank field, typing 'F1', the help key, produces a pop-up window that contains both radiologists original and discrepant responses.

3) How do the radiologists know an image needs to be adjudicated?
Both pairs of radiologists can find out which images need adjudication by viewing the DMS reports 'DMSA Adjudication Report', or the 'VCUG and Ultrasound Adjudication Report'. This report will list each scan (ID, contact occasion, sequence number) needing adjudication, and the fields requiring adjudication.

Recall that field names in the system correspond to the form name, and the question number on the form. Example DM1A2 refers to the DMSA Results form, version A, question #2.

The adjudicator (Majd or Ziessman) also knows what images require adjudication through access to the 'Query Resolution' function in the DMS. All images (identified by ID, CO, Seqno) requiring adjudication is listed in the left hand hierarchical menu (similar to the 'Data Entry' function).

4) What is the process for the radiologist to adjudicate?
One of each pair of radiologist is predetermined to be the adjudicator. It is expected that adjudication is done over the telephone with both radiologists communicating during the process. In this way, the adjudicator can document rules and standards that are derived during the process. Documentation of these rules and standards will be needed to assure consistency of image assessments throughout the study, and provide information on the process for future manuscripts.

5) How does the 'Query Resolution' system work to allow adjudication?
Adjudications and the entry of data resolutions are performed in 'Query Resolution' mode in the DMS. This is one of the features offered when you enter the CUTIE DMS. It is very similar in look and appearance to 'Data Entry' mode.

Only the adjudicator has access to records in 'Query Resolution, and accesses them using the familiar hierarchical menu on the left hand side. This menu only lists records needing

Appendix 3.2 – CUTIE Image Adjudication FAQ adjudication. The 2nd radiologist cannot access these records, but is able to go into 'Data Entry' and browse his original image assessment during the adjudication procedure.

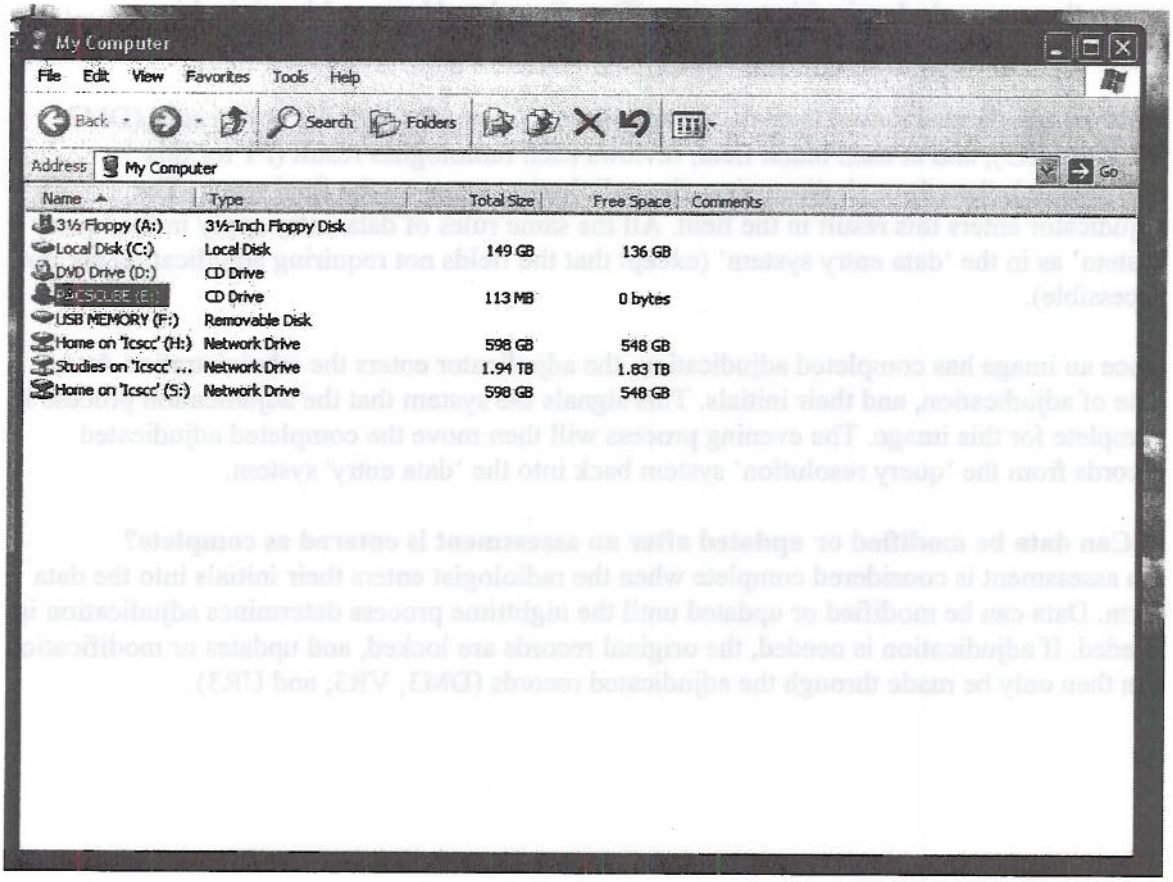
Once an adjudicated record is open, the adjudicator moves through the new record (DM3, VR3, or UR3), and at each blank field, reviews each radiologists result (F1 for this information), then through discussion, the radiologists agree on the final result. The adjudicator enters this result in the field. All the same rules of data entry apply in the 'query system' as in the 'data entry system' (except that the fields not requiring adjudication are not accessible).

Once an image has completed adjudication, the adjudicator enters the administration data, date of adjudication, and their initials. This signals the system that the adjudication process is complete for this image. The evening process will then move the completed adjudicated records from the 'query resolution' system back into the 'data entry' system.

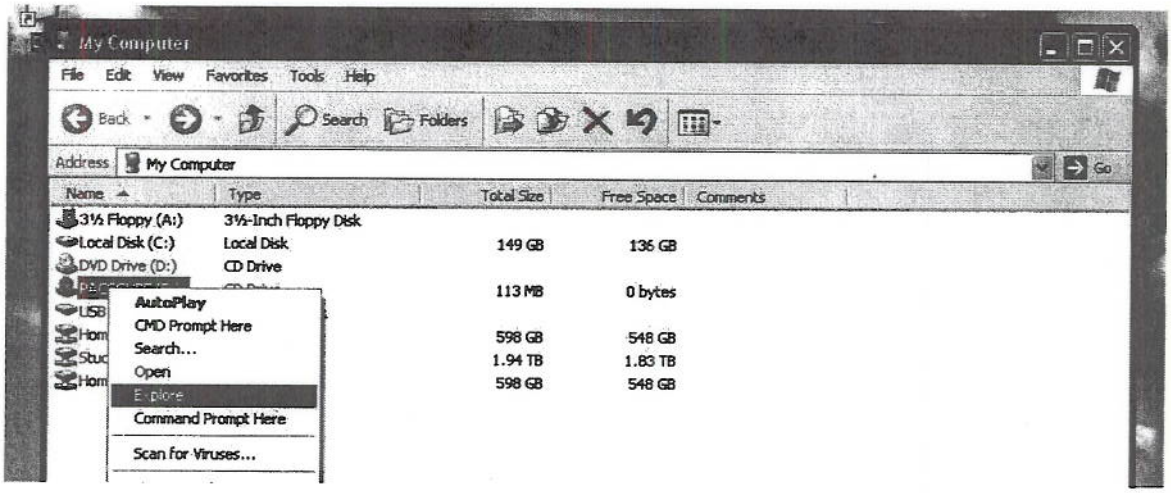
6) Can data be modified or updated after an assessment is entered as complete?
An assessment is considered complete when the radiologist enters their initials into the data form. Data can be modified or updated until the nighttime process determines adjudication is needed. If adjudication is needed, the original records are locked, and updates or modification can then only be made through the adjudicated records (DM3, VR3, and UR3).

Appendix 3.3: Zipping and Encrypting with Winzip Pro 11.2 for CUTIE Study

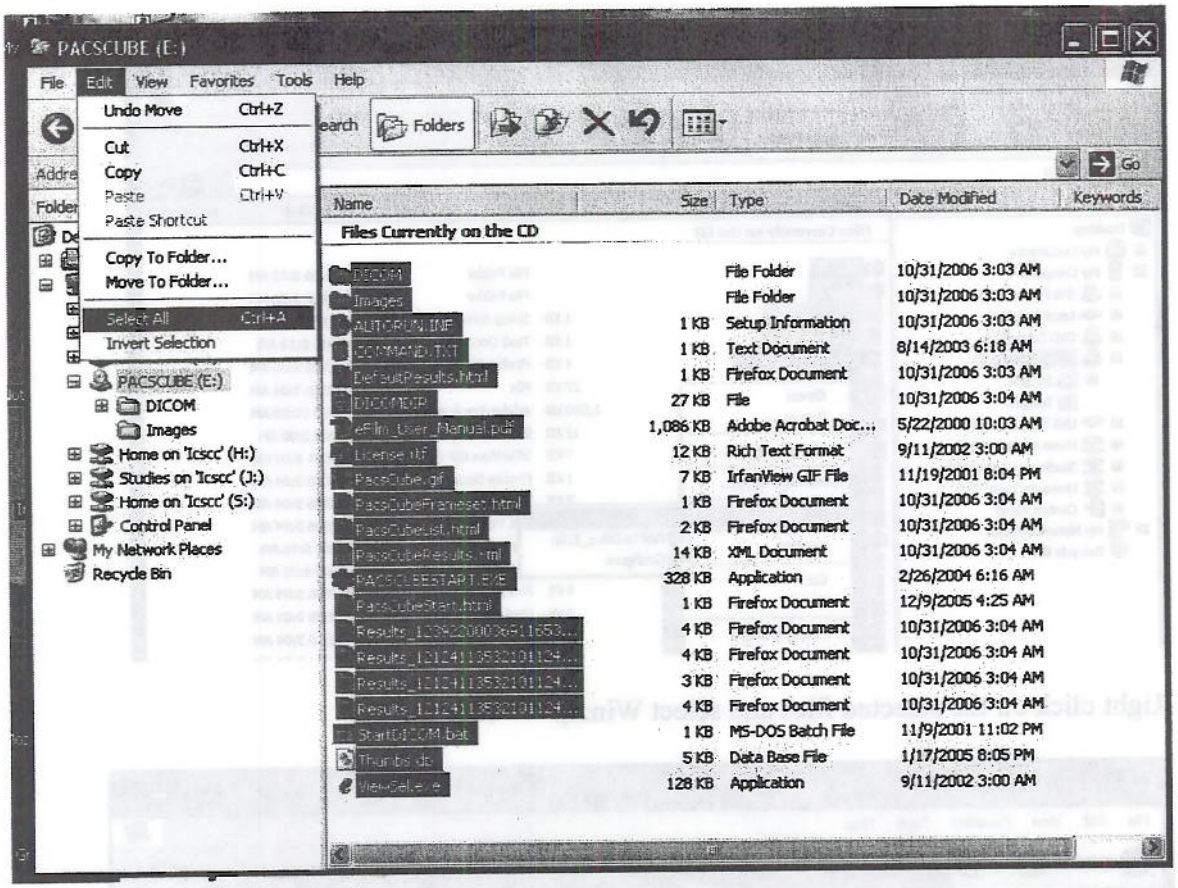
Insert radiology cd into your computer.



Open "My computer" from the Start Menu

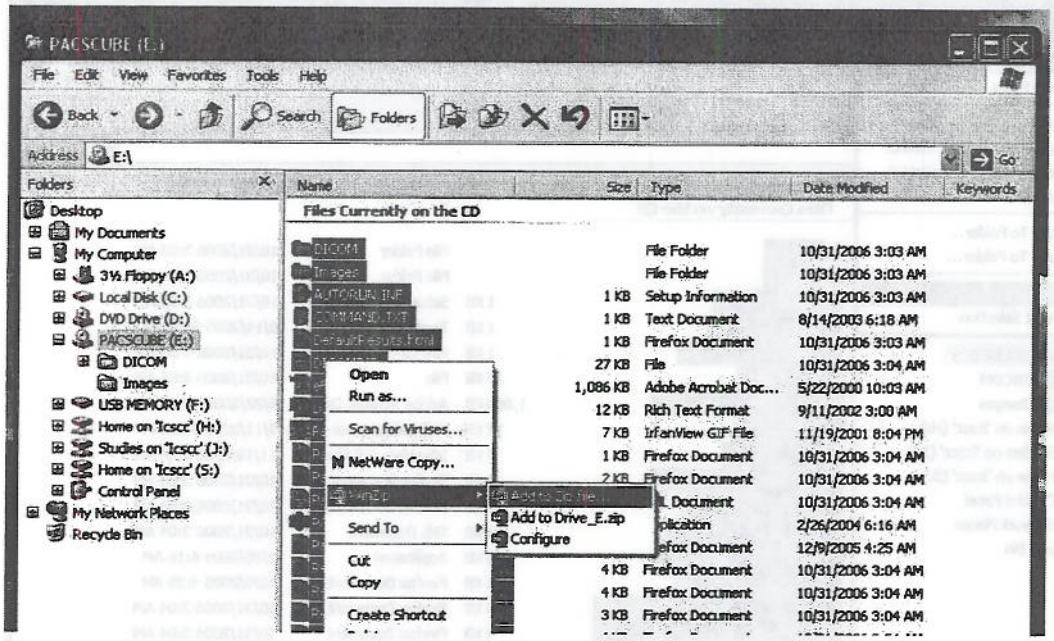


Appendix 3.3: Zipping and Encrypting with Winzip Pro 11.2 for CUTIE Study

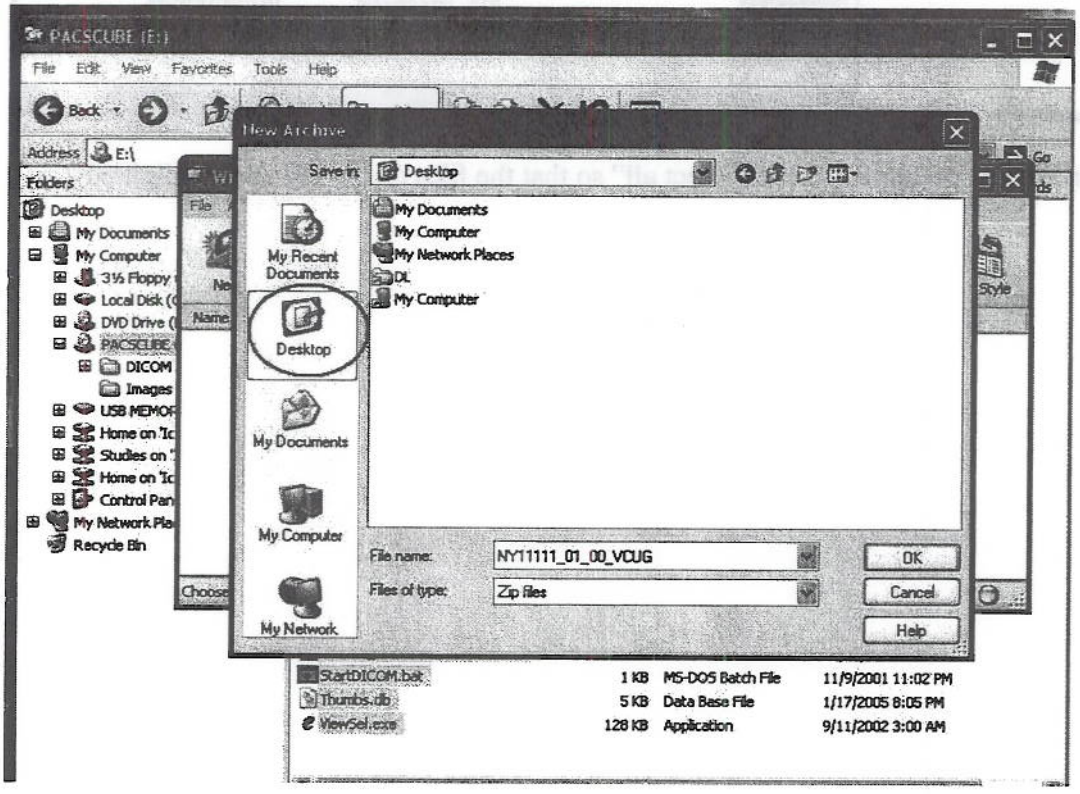


Click on the edit menu and select "Select all" so that the files on the CD are highlighted

Appendix 3.3: Zipping and Encrypting with Winzip Pro 11.2 for CUTIE Study

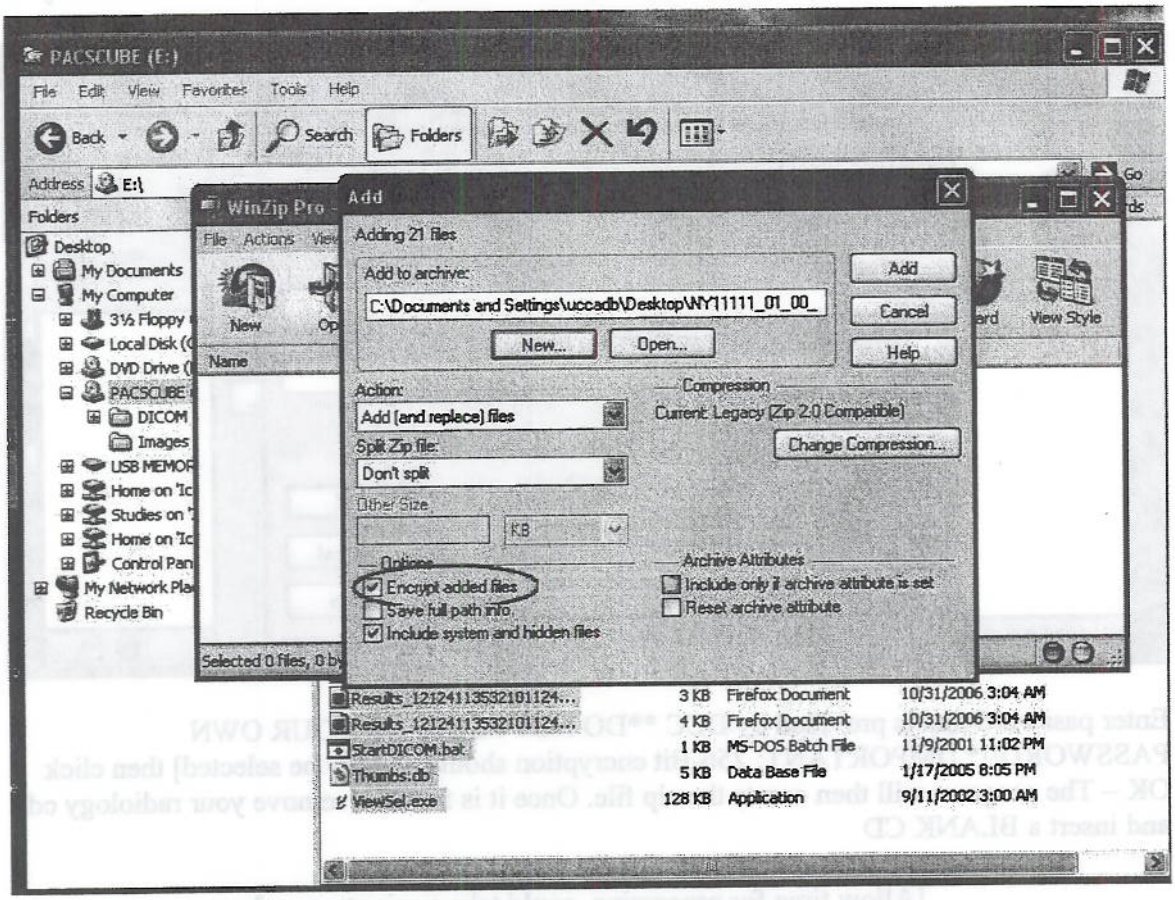


Right click on the selected files and select Winzip -> "Add to Zip"

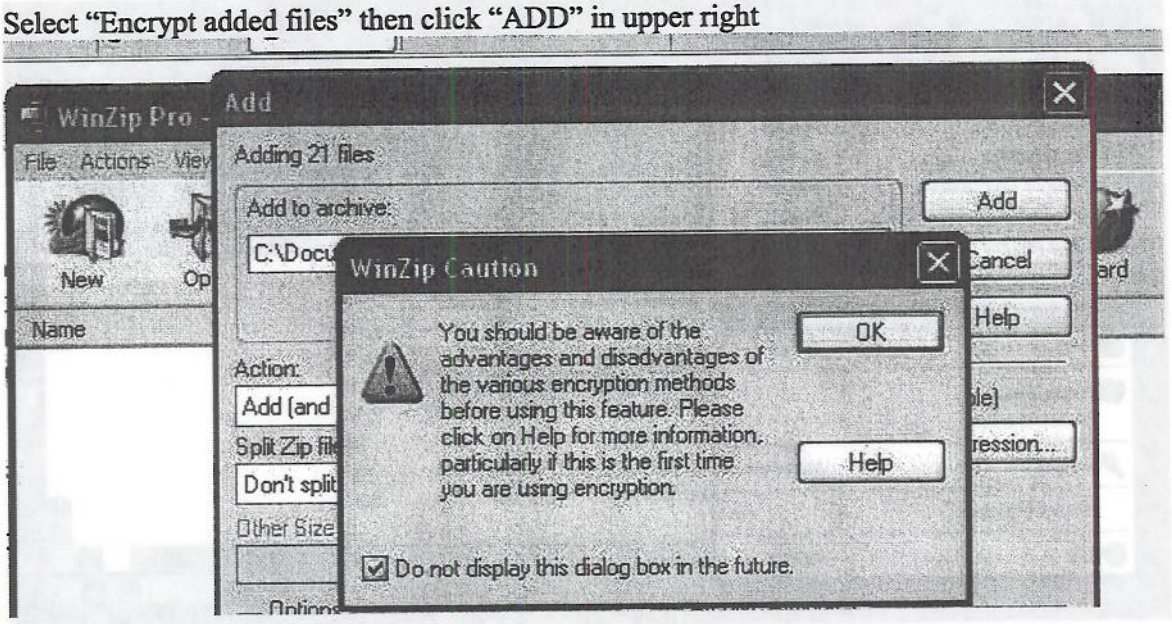


Click on "Desktop" on the left and then name your file: USERID_CO_SQ_Type where: Co= Contact Occasion, SQ = Sequel Number, and Type = VCUG, ULTRA or if both VCUG_ULTRA – Click OK once file is named.

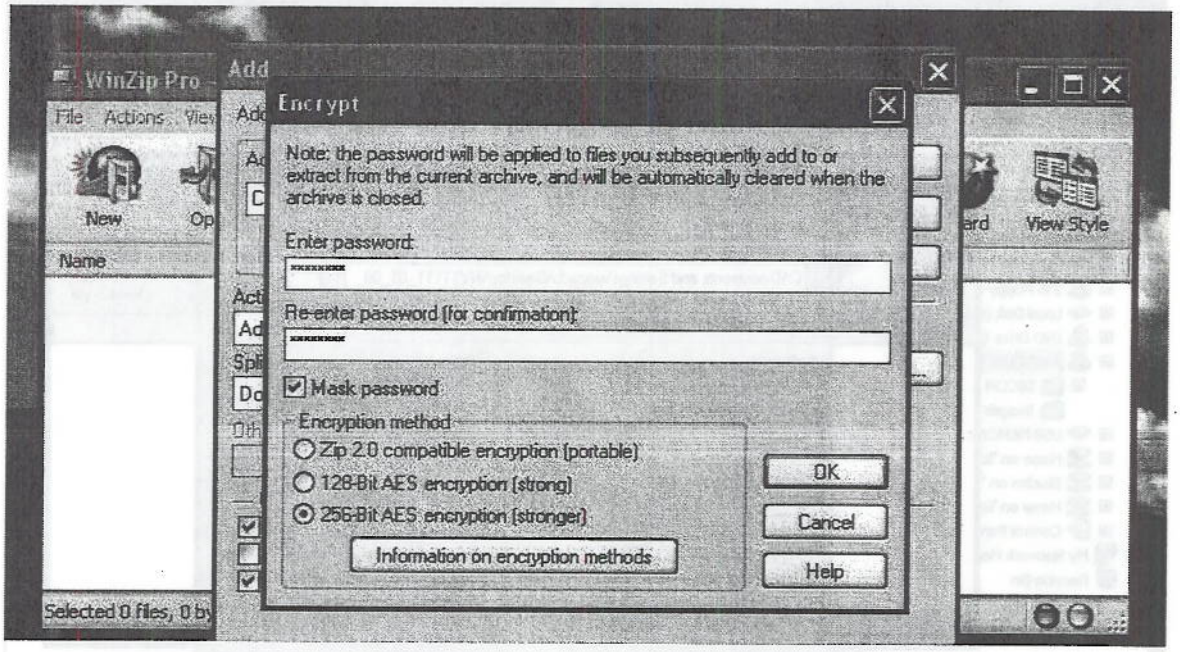
Appendix 3.3: Zipping and Encrypting with Winzip Pro 11.2 for CUTIE Study



Select "Encrypt added files" then click "ADD" in upper right

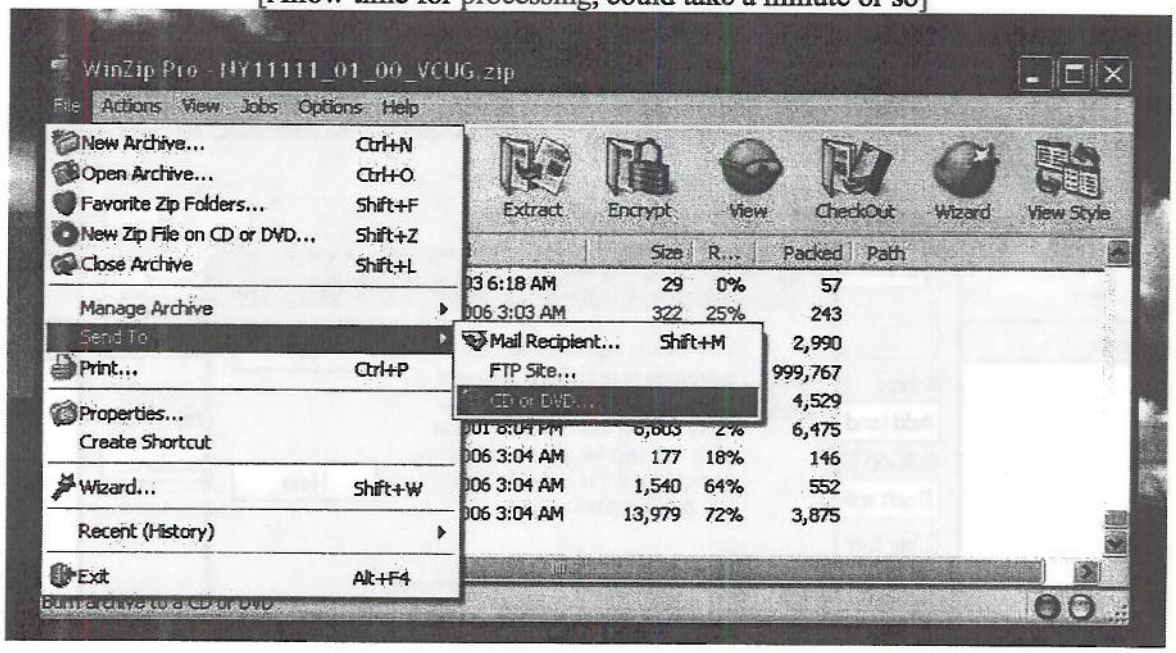


Appendix 3.3: Zipping and Encrypting with Winzip Pro 11.2 for CUTIE Study



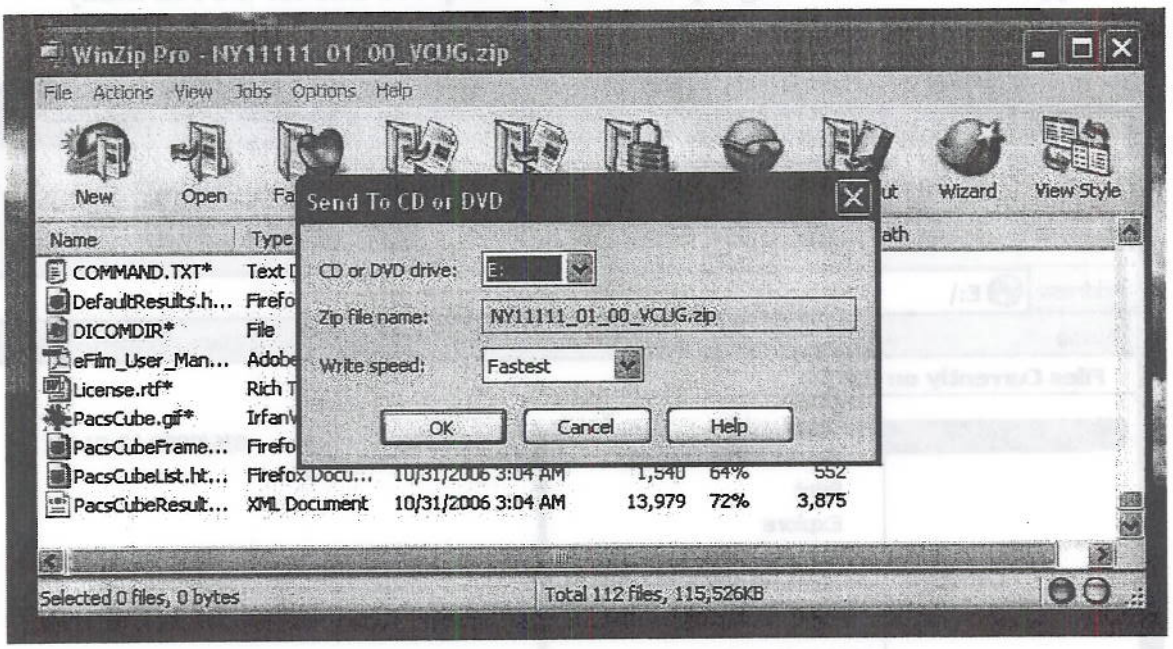
Enter password that is provided by DCC **DO NOT MAKE UP YOUR OWN PASSWORD!!* [IMPORTANT: 256-Bit encryption should already be selected] then click OK – The program will then create the zip file. Once it is finished remove your radiology cd and insert a BLANK CD

[Allow time for processing, could take a minute or so]



From the File menu select Send to-> CD or DVD

Appendix 3.3: Zipping and Encrypting with Winzip Pro 11.2 for CUTIE Study



Select the the CD or DVD drive letter that corresponds to your drive. Click OK
[Allow time for processing. Could take a couple of minutes to write each CD.]

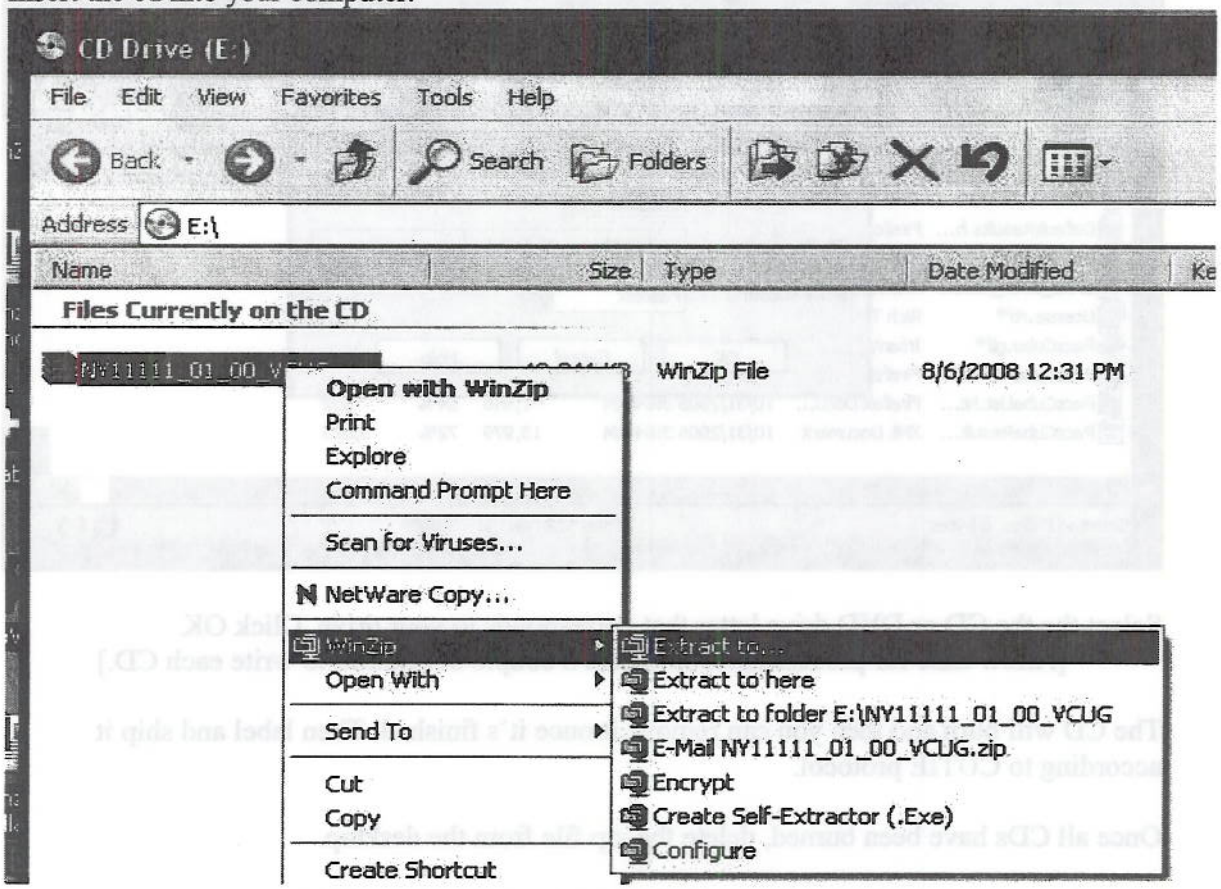
The CD will burn and then you can remove it once it's finished. Then label and ship it according to CUTIE protocol.

Once all CDs have been burned, delete the zip file from the desktop.

If you have any questions please call the DCC at 1-866-257-7242.

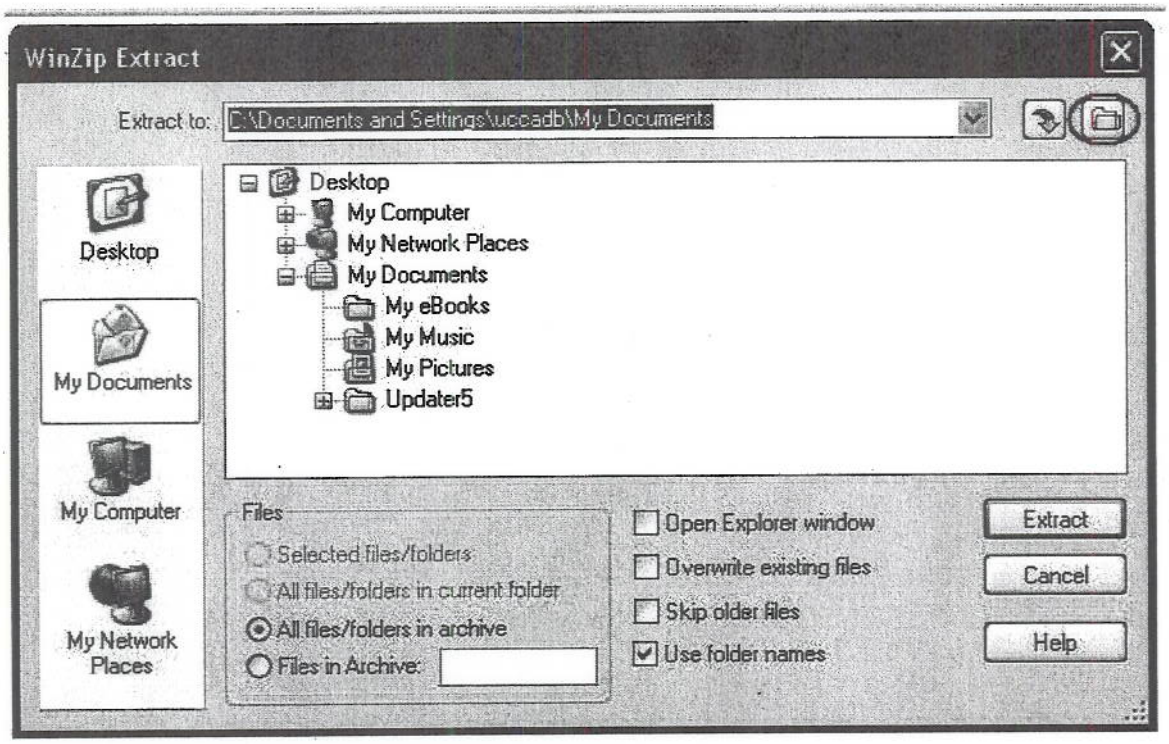
Appendix 3.4: Extracting Zip Files with Winzip Pro 11.2 for CUTIE Study

Insert the cd into your computer.

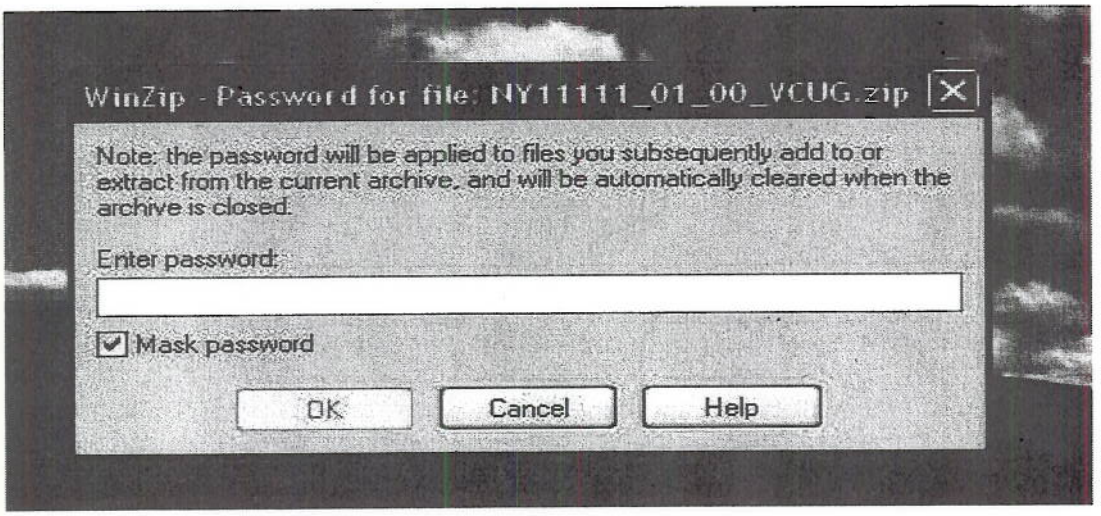


Open your CD drive from the My computer menu.
Right click on the zip file on the CD and select Winzip -> "Extract to"

Appendix 3.4: Extracting Zip Files with Winzip Pro 11.2 for CUTIE Study

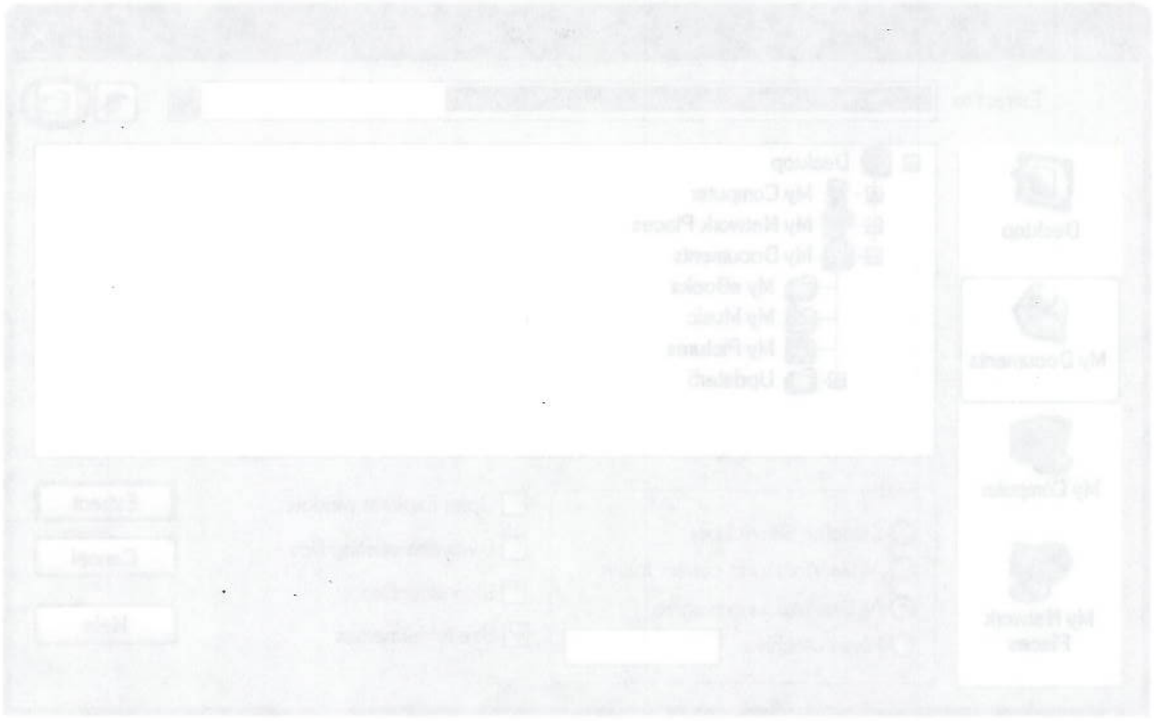


Select where you would like to extract the files to. To create a new folder select the folder icon from upper right (red circle). Click "Extract"



The files will be extracted to the location you specified and ready to be read.

If you have any questions please call the DCC at 1-866-257-7242.



Chapter 4: Enrollment and Baseline

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Baseline Visit Specimen Collection Scheme

Chapter 4: Enrollment and Baseline

4.1 Overview

The goal of recruitment and eligibility determination is to enroll eligible children as quickly and efficiently as possible for inclusion into the study. The overall goal of CUTIE is to enroll 360 children (180 per arm) over a 24-month recruitment period.

This chapter describes the procedures, data collection forms, and the ordering of procedures and data collection that must be followed for enrollment and baseline data collection.

4.2 Prior to the Enrollment Visit

4.2.1 Initial screening and Informed Consent (ICT)

Prior to enrollment, all potential participants must be initially screened, have local renal ultrasound and VCUG results (with images and VCUG sedation information), and been appropriately treated for their first or second $_{F/S}$UTI.

Informed consent procedures must be completed with the child's parents or legal guardian prior to enrollment.

Refer to Chapter 2: Recruitment, Screening and Eligibility for full details on eligibility, inclusion and exclusion criteria, and the process of informed consent.

4.2.2 Modification of Informed Consent

A participant may modify their Informed Consent at any time during the study. If a participant indicates a change in their consent to participate in the study, complete another Informed Consent Tracking Form (ICT).

4.3 Enrollment and Baseline Components

The primary objective of the baseline visit is to re-confirm eligibility and obtain baseline information and specimens. The baseline visit is composed of the following parts:

1) Re-assessment of all inclusion and exclusion criteria
2) Enrollment using the web-based DMS during entry of the EEF forms
3) A brief physical examination
4) Collection of participant demographic characteristics and medical history
5) Collection of concomitant medication data
6) Collection of baseline blood and urine
7) Parental completion of the self-administered questionnaires

4.3.1 Data Collection Forms

The data collection forms required to complete the baseline visit are the listed below in Table 4.1.

Table 4.1 Baseline Data Collection Forms

Forms Collected Prior to Enrollment:
- Informed Consent Tracking Form (ICT)
- VCUG Sedation Form (VSF)

Forms Collected During Baseline Contact:
- Eligibility and Enrollment Form (EEF)
- Baseline Demographic Form (BDF)
- Physical Exam Form (PEF)
- Baseline Medical History Form (BMH)
- Concomitant Medication Listing/Coding Form (CMF)
- LIA (Life Impact Assessment) Questionnaire (LIQ)
- Dysfunctional Voiding Questionnaire (DVQ) – if toilet trained
- Specimen Collection Form (SCF)
- Participant Contact Form (PCF) *
- Biospecimen Repository Shipping Log (NIDDK-USL) *
- Genetics Repository Shipping Log (NIDDK-BSL) *
- VCUG / Ultrasound Inventory and Shipping Log (VUS)

Forms Completed after the Baseline Visit (though still contact occasion = 01)
- Blood Specimen Results Form (BSR)
- Urine Specimen Results Form (USR)
- DMSA Sedation Form (DSF), unless collected prior to baseline
- DMSA Imaging Inventory and Shipping Log (DSS)

Reference Radiologist Forms (completed and entered by the radiologists)
- Ultrasound Results Form (URF)
- VCUG Results Form (VRF)
- DMSA Results Form (DMF)

* Not data entered

4.3.2 Ordering of Data Collection during the Visit

Sites may organize the Baseline data collection to accommodate their own staffing and organization needs. There are, however, a few things that are required and need to be considered:

1. Consent must be obtained and the ICT entered prior to any study data collection or enrollment.

2. A urine dipstick negative for pyuria is required prior to enrollment to assure no new infection is present. If pyuria is positive on dipstick (leukocyte esterase $\geq$ trace), a

negative WBC (**WBC < 10 WBC/mm^3 or WBC < 5 WBC/hpf**) obtained on this same urine may trump the dipstick to document absence of pyuria. At this same time, urine for local chemistries (creatinine and microalbumin) and repository storage should also be collected.

3. Weight measurement during the physical exam must have been taken prior to blood specimen collection.

4.3.3 Data Entry during Visit

CUTIE data collection can be recorded on paper data collection forms, or entered directly online into the CUTIE data management system (DMS). Four forms are required to be entered at the enrollment/baseline visit: the ICT must be entered as documentation of participant consent, and the EEF must be entered to enroll the participant.

All other data collection forms can be entered after the clinic visit is completed. The DCC requires all data collection forms to be entered within 5 working days of data collection.

4.4 Enrollment

The process of enrolling participants in CUTIE is the official confirmation of all eligibility criteria, and a final ruling out of potential exclusions.

In order to enroll a child, he or she MUST be present in the clinic. You cannot run the eligibility algorithm in the web-based data management system prior to the clinic visit.

4.4.1 Verifying no new UTI prior to Enrollment

Prior to enrollment, you must verify that the child has not experienced a temperature (≥100.4°F or 58°C) anytime in the last 24 hours; this could be done by a telephone call the day before the scheduled visit. If the child has been sick with fever, the Coordinator will need to verify that this is not another UTI. Enrollment must be rescheduled.

A urine dipstick test must also be pEEFormed and be negative for pyuria. In the event that the dipstick is positive for pyuria, that same urine may be spun and checked for the presence of WBC using microscopy. If pyuria is present, you must obtain catheterized urine specimen for culture to verify that the child does not currently have a UTI. This would require rescheduling of the enrollment and baseline data collection. If the urine culture results are negative, the child should be scheduled for enrollment. During the enrollment, the urine should be dipped for pyuria, but the child may be enrolled, even if pyuria is present at the second attempt of enrollment.

4.4.2 Eligibility and Enrollment Form (EEF)

Eligibility verification is completed upon data entry of the EEF form, at this enrollment visit. You may have used this form initially as a tool to pre-screen or screen the child for consideration. However, it is critical that this form is completed appropriately at **this** clinic

visit to officially verify all eligibility criteria. Some criteria may have changed since pre-screening and screening.

Particular attention must be made to accurately assess the number of UTI's that the child has experienced. The child is eligible for CUTIE if they have had 1 or 2 UTI's. In the event that more than one UTI has occurred, in order for the child to be eligible, he/she may not have been treated with prophylactic anti-microbials nor had a VUR diagnosis. The UTI immediately preceding the enrollment into CUTIE will be called the index UTI. You must have medical record documentation of the diagnosis of the index UTI, documentation of fever or symptoms occurring within ±24 hours of the beginning of the index UTI workup, and documentation showing appropriate treatment for at least 7 days with an effective drug.

Refer to Chapter 2: Recruitment, Screening and Eligibility, and the EEF QXQ for specific details regarding eligibility and the EEF form.

At the time of enrollment, verify that the child is at least 2 months of age, and less than 72 months and the index UTI had occurred within 112 days of enrollment. All VCUG and U/S images must be collected prior to enrollment, must also have been collected after the index UTI and within the 112 days of the enrollment date. The baseline DMSA must be collected within 2 weeks of enrollment and no more than 112 days from the index UTI.

4.4.3 The Enrollment Procedure

Enrollment occurs during the data entry process of the EEF form.

Refer to Chapter 2: Recruitment, Screening, and Eligibility for specific details on eligibility and the EEF form.

4.4.3.1 Enrollment Procedure Using the Data Management System

The Coordinator enters the data from the EEF into the DMS. As the EEF form is data entered, the DMS will validate all responses. If an edit fails, the DMS will provide an automatic query message and skip the entry to the end of the form, bypassing the enrollment. If all edits pass, the form asks "Do you wish to enroll this child into the CUTIE Study?" Entering a "Y' in this field enrolls the child.

The eligibility/enrollment program verifies the patient's eligibility status based on the entered responses. At this time the system will let you know that the enrollment was successful..A successful enrollment will automatically send an email to the DCC notifying them of the enrollment.

In the event that the enrollment program aborts and does not run, you will receive an error message explaining the reason for the random information in the EEF. Make the necessary corrections to the EEF begin the enrollment procedure again.

4.4.3.2 Enrollment when the Data Management System is Not Functional

Since the enrollment procedure requires entry through an internet connection, a backup procedure is necessary for cases in which the clinic's computer system is not functional, or the WEB is inaccessible or not operating appropriately.

As soon as it is realized that an enrollment is anticipated and the DMS is nonfunctional, contact the DCC to arrange a remote enrollment. Emergency enrollment procedures will be done over the phone with the DCC.

- All necessary data collection forms must be completed on paper.
- The Eligibility and Enrollment Form (EEF) must be completed to provide final assessment, verification, and review of enrollment eligibility.
- The Physical Exam Form (PEF) must be completed to provide the weight measurement for dosing.
- The Study Coordinator (or other appropriately trained staff member) can call the DCC at 866-257-7242, normally staffed from 8AM – 5PM EST, Monday through Friday. Enrollments at other times must be arranged in advance.
- The DCC must receive faxed copies of completed EEF and PEF data collection forms prior to the enrollment call.
- Participant baseline data collection can be ongoing while the process of emergency enrollment is being completed.

First, the DCC will attempt to solve the computer problem, if it relates to the CUTIE DMS. If this fails, the Study Coordinator and the DCC will review the participant's eligibility forms over the phone, and obtain the participant's weight. The DCC will then enroll the participant. (**Note:** Since chances for error are increased by transmitting eligibility data over the phone, this system should only be used when absolutely necessary.)

As soon as the system at the clinical center becomes operational, entry of the EEF and PEF must be completed in the DMS system BEFORE ANY FURTHER ENROLLMENTS CAN OCCUR, and the contact person providing the phone enrollment must be notified that this has happened. It is essential to enter any remote enrollments into the CUTIE DMS in the order in which they were enrolled by phone, before using it for any further enrollments.

4.5 Baseline Data Collection

Baseline data is collected in order to adequately describe the population in the trial. This includes demographic variables of gender, ethnicity and race, and includes socio-economic factors such as income and education. Some baseline data includes collecting known factors that may influence the outcome, such as concomitant medications being taken by participants, and medical history information.

Baseline data collection can be obtained in any order that is efficient at the clinical sites. Except for urine collection (required for final eligibility assessments) it is recommended that

the blood specimens not be collected prior to enrollment. Any baseline data collected prior to enrollment will have to be repeated if the enrollment is rescheduled.

4.5.1 Physical Exam (PEF)

The physical exam includes temperature, blood pressure, height and weight measures as well as a short abdominal exam, all reported on the Physical Exam Form (PEF). The weight measurement taken during the physical exam will be used to assess the amount of blood drawn for laboratory specimens.

Refer to the PEF QxQ for item-specific instructions regarding administration.

4.5.2 Baseline Data Collection Interviews

Much of the baseline data collection is done through interviewing the parent/guardian. Parent/Guardian interview forms include the Baseline Demographic Form (BDF), the Baseline Medical History Form (BMH) and the Concomitant Medication Form (CMF).

Section 13.9 of Chapter 13: Data Management and Administrative Procedures, includes techniques for conducting questionnaire interviews.

Refer to the QxQ documents for the BDF, BMH, and CMF for item specific instructions regarding administration.

4.5.2.1 Concomitant Medication Form (CMF)

Concomitant medications are often collected on patients involved in a research study. This data is collected based on parent/guardian's report. Parents will be requested to bring in medication bottles of any medications their child is currently, or has taken since the last contact, or to record and bring in this information in the Participant Handbook/Diary.

Of particular interest are anti-microbial medications in addition to any other prescription medications for chronic conditions, or medications for constipation or over-active bladder. At baseline, only those medications currently being taken and the prophylactic antimicrobial the child had been taking following his/her UTI diagnosis will be recorded along with the start dates for the medication(s). In the case of the antimicrobial prophylaxis taken prior to enrollment, the date the medication was completed will be the day of enrollment.

Concomitant medications are coded in order to summarize the data by a preferred term. Coding of concomitant medications is assigned into the DMS at the time of CMF data entry, using a drug dictionary lookup table in the DMS. The CMF form will be data entered at every CUTIE protocol-scheduled contact.

Refer to the CMF QxQ for more instructions on reporting concomitant medications including instructions on coding a stop date for continuing medications, and Chapter 14: DMS User's Guide for information on coding.

4.5.3 Self-Administered Forms

4.5.3.1 Life Impact Assessment Questionnaire (LIQ)

The Life Impact Assessment Questionnaire (LIQ) is a quality of life and resource utilization instrument that is a self-administered questionnaire for the parent/guardian to complete. This questionnaire can be administered with help, and must be used with an interpreter for families who do not speak English.

Refer to the LIQ QxQ for form specific instructions.

4.5.3.2 Dysfunctional Voiding Questionnaire (DVQ) and the DES Treatment Form (DTF)

The DVQ questionnaire derives from a standardized scale and is designed to evaluate voiding dysfunction and assess constipation. This is a self administered questionnaire for the parent/guardian to complete with their child, if their child is already toilet/potty trained. The questionnaire is intended to obtain information about the child and is worded for a child respondent. This questionnaire can be administered with help, and must be used with an interpreter for families who do not speak English.

After the DVQ has been completed by the family, the Coordinator should run the DMS report entitled DVQ Score Report. The report will yield the score of the dysfunctional voiding instrument. If the DVQ score for a girl is >6, or for a boy >9, the DES Treatment Form (DTF) should be collected on the participant. The DTF is designed to give information on DES treatments.

A child is considered toilet/potty trained when he or she is urinating and defecating in the toilet or potty by themselves during the day.

Refer to the DVQ QxQ for form specific instructions.

4.5.3.3 Challenges with Self Administered Questionnaires

In any survey, whether interview or self-administered, comprehension of the question is the first challenge. However, the task is different in a self administered survey. In a self-administered survey, respondents must first perceive the information before they can comprehend it. Once respondents perceive the information, they must comprehend the layout (the visual aspect) of the information as well as the wording (the verbal aspect). Furthermore, respondents must comprehend much more than just the wording of the survey questions and response categories.

In a self-administered survey, respondents are often given introductory material and instructions. They must comprehend the instructions or directions that are meant to guide them through the questionnaire. In an interviewer-administered questionnaire, the interviewer plays a critical role in this perceptual process. In contrast, the entire onus of perception is on the respondent in a self-administered format.

When respondents are asked to complete a self-administered questionnaire, they are being asked to perform a task that from their perspective may be different from the task we wish them to perform. From the respondent's perspective, the task may be similar to asking them

to view a picture, in which they are free to start anywhere and to make their own decisions as to which parts of the picture to examine in what order.

However, from our perspective, this viewing method is detrimental, for it gives us very little control over the perceptual process. From our perspective, it would be best if respondents started at a specified place, read prescribed words (in order to comprehend the question or stimulus) in the order in which we intend, provide answers to each stimulus, and move sequentially through the questionnaire. In general, we do not want respondents to mark answers without having fully read and understood the questions and accompanying instructions, nor do we want them to pick and choose which questions get answered and in which order.

Advantages of self-administered questionnaires include anonymity and privacy which may encourage more candid and honest responses, and lack of interviewer imposed biases. They are attractive in that they can be given to a respondent to complete while staff continues with other necessary tasks. However, disadvantages include no interviewer intervention available for probing or explanation, respondents may feel they cannot ask for clarification, and respondents are more likely to stop participating mid-way through a self administered questionnaire.

For these reasons it is important that the Coordinator remain accessible to the parent/guardian during the DVQ and LIQ completion. Instructions on how to appropriately fill out the form should be provided, asking that respondents start with the first question and work down through the form, completing all questions as best they can. Let the parent/guardian know that there is no right or wrong answer to these questions. It is acceptable to provide clarification on words or questions within these forms when necessary. However, parents/children should be encouraged to respond based on their personal experience and the way they think the answer best applies to them.

4.5.4 Laboratory Specimen Forms

4.5.4.1 Baseline Specimen Collection (SCF)

Refer to the detailed procedures on specimen collection, identification, processing, and shipping documented in Chapter 5: Specimen Collection. Specimen collection and shipping is documented on the Specimen Collection Form (SCF). The SCF QxQ provides specific item instructions.

Urine specimens must be collected at the baseline visit on each participant. The urine collection should have occurred prior to enrollment as part of the eligibility check verifying pyuria does not exist at the time of enrollment. All other specimen collections should occur after eligibility is verified through entry of the EEF form and enrollment. Blood collection, also a part of baseline collection, can be scheduled during the DMSA imaging if this occurs after the enrollment visit. Section 5.5.3 in Chapter 5 Specimen Collection, describes the blood specimens to be collected, and the priority of collection.

4.5.4.2 Baseline Specimen Shipping Logs

Specimens shipped to central labs or repositories must also have shipping logs completed. These logs are mailed with the specimens, providing an inventory of the shipment. They are not data entered.

There are three specimen shipping logs:

- Biospecimen Repository Shipping Log (NIDDK-USL)
- Genetics Repository Shipping Log (NIDDK-BSL)
- Central Blood Lab Shipping Log (CSL)

4.5.5 ~~Medication Dispensing and Dosing Form (MDD, MDL)~~

The CUTIE Study does not have any study medication.

4.5.6 Radiographic Images (VSF, VUS, DSF, DSS)

Results of the renal/bladder ultrasound and VCUG are required as part of the study eligibility criteria, and must be completed prior to enrollment for eligibility criteria, and within 70 days after diagnosis of the index UTI. In addition, a Baseline DMSA scan is required for all participants. The Baseline DMSA must be completed within 2 weeks of enrollment (before or after), and no more than 10 weeks (70 days) after diagnosis of the index UTI. Some participants may already have had the DMSA study completed at the time of enrollment. If the Baseline DMSA has not already been performed at the time of enrollment, the Coordinator should schedule one immediately, in order to adhere to the 8-week window.

Images of all three scans are required, as are the local reading reports, and information on sedation used during the VCUG or DMSA. Data collection forms VSF and DSF are required to document sedation use (or non-use) during the procedures. Data collection forms VUS and DSS are required to document the shipping of images to the study reference radiologists.

Refer to Chapter 3: Radiology Imaging for detailed study procedures, forms required, and shipping instructions to the reference radiologists. Baseline images should not be shipped prior to enrollment, but should be shipped within a week of enrollment, or within a week after having a scan performed.

Note: DMSA images collected during a participants' follow-up, and especially after a UTI, follow a different shipping schedule due to the time urgency of these images.

4.6 Participant Handbook/Diary

Each participant's parent/guardian is to be given a participant handbook/diary, and a CUTIE Participant Follow-up Schedule (a DMS report). The handbook provides a summary of procedures associated with each follow-up contact. The handbook also functions as a diary for recording any fever or illnesses, medical care visits, and changes in concomitant medications that need to be reported to the Coordinator at each follow-up contact. Other important information and instructions for the parents regarding their child's participation in the study is also documented in the handbook. The Coordinator should review the handbook with the parent/guardian and instruct them on the use of the diary.

4.7 Participant Contact Information (PCF)

The Participant Contact Form (PCF) provides vital contact information on each enrolled participant, his or her parent/guardian, and a second backup contact person. The participant's primary physician is also recoded along with his or her contact information.

This form should be completed by study personnel with the parent/guardian present, providing the information. Contact information on previously obtained medical records may not be current. All sections for which the participant is willing and able to provide information should be completed. It is critical to obtain information for an additional 2nd "contact person", who will know the health status and/or location of the participant in the event that they are difficult to follow-up with.

This form is not data entered, and should be stored with other confidential materials to maintain the confidentiality of the study participants. If your clinic or hospital has a system in place that collects this information (including 2nd contact person), you will not need to complete this study form, however, you will need to be able to demonstrate that this information is readily available to you during a monitoring visit.

4.8 Scheduling follow-up Contacts

At each contact, the Coordinator should make a point of scheduling the next two study contacts. At the baseline visit, this would be telephone contacts at two and four months of follow-up since enrollment. Contacts are expected within a 20 day window, 10 days on either end of the target date (target date is determined based on the number of months since enrollment).

The DMS contains a CUTIE Participant Follow-up Schedule Report that lists all follow-up contact target dates, contact type (telephone or clinic visit), and the protocol allowed contact window. A copy of this report would have been first provided to the parent/guardian at the time of enrollment, and the information may have been written into the patient handbook/diary.

CUTIE would rather have data outside the time period than no data at all, but it would be a waste of resources to schedule two contacts too close together. Scheduled contacts for enrolld participants should be at least 30 days apart.

4.9 Local laboratory results (BSR, USR)

Reporting of local laboratory results will most likely occur after the participant's clinic visit when results are received in the CUTIE clinic.

Data from the local lab reports are to be transcribed/entered into the Blood Specimen Results Form (BSR) and the Urine Specimen Results form (USR).

Refer to the BSR and URF QxQ for form specific instructions.

4.9.1 Alert Notifications

If clinically significant findings are identified in the local laboratory reporting, Coordinators must promptly notify the participant's primary care provider. In addition, Coordinators must complete an Adverse Events Form (AEF) for the clinically significant findings.

Refer to Chapter 9: Participant Safety and Adverse Event Reporting for procedures related to laboratory alerts

Appendix 4.1 – Baseline Visit Checklist of Procedures and Forms

CUTIE

Careful Urinary Tract Infection Evaluation

Baseline Visit Checklist

Preparations		Associated Forms
Participant Contact Information (preliminary)		PCF
Urine culture and urinalysis results from index UTI		
Baseline and ultrasound report (performed within 16 weeks after diagnosis of index UTI)		
Baseline VCUG scan report (performed within 16 weeks after diagnosis of index UTI)		VSF
Medical records and reports from index UTI		
Task / Procedure		Associated Forms
Begin with…	Informed Consent	ICT
Items that must be performed in the specified order	1. Physical Exam	PEF
	2. Study Eligibility and Enrollment	EEF
Data to be collected at anytime during the visit	Participant Contact Form	PCF (paper only)
	Baseline Demographic Form	BDF
	Baseline Medical History	BMH
	LIA Questionnaire	LIQ
	DV Questionnaire (if toilet trained)	DVQ
	Concomitant Medications	CMF
	Participant Handbook / Diary	
	Copy of signed consent form	
Specimen Collection (see reverse)	Urine Collection (collected at enrollment)	SCF, USR, BSR, NIDDK-USL, NIDDK-BSL
	Blood Collection (collected within 14 days of enrollment)	
Baseline Imaging	Baseline DMSA scan (performed within 16 weeks after diagnosis of index UTI and within 2 weeks after date of enrollment)	DSF, DSS
	Baseline VCUG and Ultrasound scans shipping	VUS

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Appendix 4.2 – Baseline Visit Specimen Collection Scheme

CUTIE

Careful Urinary Tract Infection Evaluation

BASELINE Specimen Collection Scheme

Urine Collection – Collect at Baseline

A. Dipstick

If leukocyte esterace Negative (-)
(Proceed with normal randomization)

B. Order local **microalbumin** & **creatinine** on collected urine

C. 4-10 ml in orange-top cup, unfrozen
⇨ Ship to **Biosample Repository** (U label)

If leukocyte esterase Positive (trace to +++)*
Collect catheterized or clean-catch specimen & dip again for leukocyte esterase (LE)

If LE negative (-)
Proceed with normal randomization steps B & C to the left.

If LE positive (trace to +++)*
B. Order culture to determine if recurrent UTI
C. Tentatively reschedule randomization

* WBC count obtained on dipped urine trumps dipstick results (i.e. if LE positive on dip, but WBC is negative, then child is eligible)

Blood Collection – Collect within 14 days of Enrollment

1.5ml in yellow SS tube, aliquot serum

Priority 1: 0.5ml for **Cystatin C** and **Creatinine**
⇨ Batched & FROZEN at -70 , ship every 3 months to **Central Lab in Kansas City, MO** (C label)

Priority 2 (collect if enough in *this* SS tube): 0.1ml serum for **Electrolytes**
⇨ Send to **Local Lab** (no label)

For kids ≤ 20lb: collect ONE 3.0 ml ACD tube
For kids > 20lb: collect TWO 3.0 ml ACD tubes, $^2/_3$ full
⇨ Ship room temperature to **Genetics Repository** (B label)
If ACD tube(s) not collected at Baseline, then collect at a later clinic visit.

Collect ONLY from kids >20lb
4.0ml in yellow SS tube ⇨ ***Spin*** and Ship unfrozen (with frozen gel pack) to **Biosample Repository** (S label)

Central Lab in Pittsburgh: Karen.Barbadora@chp.edu
Central Lab in Kansas City: Nancy Wilson nwilson@cmh.edu
Genetics Repository: Dana Witt witt@biology.rutgers.edu
Biosample Repository: BIO-NIDDKRepository@thermofisher.com

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Chapter 5: Specimen Collection

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Chapter 5: Specimen Collection

5.1 Overview

Urine and blood specimens are collected for local clinic laboratory analysis. Blood serum is collected for central laboratory analysis. Among those participants who appropriately consented for DNA extraction and storage of biological specimens, additional blood and urine is collected and stored in NIDDK repositories for future studies.

Table 5.1 provides a summary of specimen collection during the study. All specimens are collected at the baseline and end-of-study clinic visits.

This chapter provides instructions on procedures for the collection, processing, shipping, and reporting of laboratory specimens. Study participants may have additional blood and urine studies as part of their routine and emergency clinical care. In the event that these data are reported at alert levels, they would need to be reported as part of adverse events or endpoint data collection, but are not normally considered part of the routine protocol specimen collection, and are not required to be collected and processed as described below.

Table 5.1 Summary of specimen collection

Type of Specimen	Baseline	6-mo Clinic Visit	12-mo Clinic Visit	18-mo Clinic Visit	End of Study Visit
Urine for local dipstick and local	X				X
Urine for Biosample repository	X				X
Blood for Local Lab*	X	X	X	X	X
Blood for central lab	X				X
Blood for Genetics Repository	X**				X
Blood for Biosample Repository	X				X

* Electrolytes at baseline and end-of-study

** If blood for genetics repository not collected at baseline, it may be collected during a later blood draw

5.2 Data Collection Forms

The required study data collection forms associated with specimen collection and shipping are listed and described below:

- Specimen Collection and Processing Form (SCF)
- Central Blood Lab Shipping Log (CSL)
- NIDDK Genetics Initiative Phlebotomy Mailing Form (NIDDK-BSL)
- NIDDK Biological Specimen Repository Mailing Form (NIKKD-USL)
- Blood Specimen Results Form (BSR)
- Urine Specimen Results Form (USR)
- Central Blood Lab Form (CLR)*

* entered at central labs

5.2.1 Specimen Collection and Processing Form (SCF)

All specimen collection is documented onto the SCF. Through this form, the DCC tracks the collection date, collection time, volume, and type of specimens collected, as well as the date of shipment to the study central labs and repositories. Anticipated results are then closely monitored. Note: this form will need to be updated to record shipping dates for those specimens not shipped at the time of collection and initial recording of the SCF. Refer to SCF QxQ for item specific instructions. Note: If baseline blood collection is split between the Enrollment visit and a Baseline DMSA visit, then a second SCF form will need to be completed to document the 2nd blood drawn. If all blood is drawn at once, then the draw is recorded on the original SCF form.

5.2.2 Central Lab Shipping Logs (CSL, RSL)

The Central Lab Serum Specimen Shipping Log (CSL) is a shipping log that accompanies specimens being sent to the study central labs. It is not data entered.

5.2.3 NIDDK Genetics Initiative Phlebotomy Form (NIDDK-BSL)

This is the NIDDK Genetics Repository shipping log, which is to be completed at the time of blood specimen collection using ACD tubes for eventual DNA cell lines. It is included in the mailer box with the specimen being shipped to the Rutgers Cell and DNA repository. In addition, a shipment notification is to be made to the Repository on the day of shipping, either by email, fax, or through the Repository web portal (as instructed on this form). This form is not data entered.

5.2.4 NIDDK Biosample Repository Mailing Form (NIDDK-USL)

This is the NIDDK Biosample Repository shipping log to be sent with the urine specimen, and serum separator tube (if child >20 lbs) to Fisher Bio-repository. The end of study visit will also collect blood in an EDTA tube which will also be included in the shipment. A shipment notification to the repository on the day the FedEx shipment is required by email or fax (see packing and shipping instructions listed on this form). This form is not data entered.

5.2.5 Blood Specimen Results Form (BSR)

This data collection form reports on the electrolyte study done at the baseline and the end-of study clinic contact. This form is data entered at the site upon receipt of results.

Any clinically significant findings in local laboratory results should be reported on an adverse event form.

5.2.6 Urine Specimen Results Form (USR)

This data collection form is used to report the urinalysis and urine culture results from baseline and end-of study data collection. In addition, coordinators will use this form to document findings during the study from medical records abstraction of urinalysis or urine culture results for potential study UTI endpoints data collection. This form is data entered at the site.

Any clinically significant findings in local laboratory results should be reported on an adverse event form.

5.2.7 ~~Rectal Swab Specimen Results Form (RSR)~~

Rectal swabs are not collected with the CUTIE Study.

5.2.8 Central Lab Blood Results Form (CLR)

This form is completed and data entered at the Central Blood Lab for cystatin-C and creatinine results.

5.3 Specimen ID labels

The DCC will supply labels for all specimen tubes and containers, as well as shipping logs, for specimens that are shipped from the sites to the study central labs and repositories. Sites are responsible for appropriate labeling and tracking of specimens analyzed locally. Locally analyzed specimens must be identified at each site in such a way that the local lab report can be easily linked to the participant study ID number.

Prior to collection, place the appropriate specimen collection label onto the appropriate collection receptacle (tube or cup). All labels will contain the following information:

- Barcode
- Participant ID number

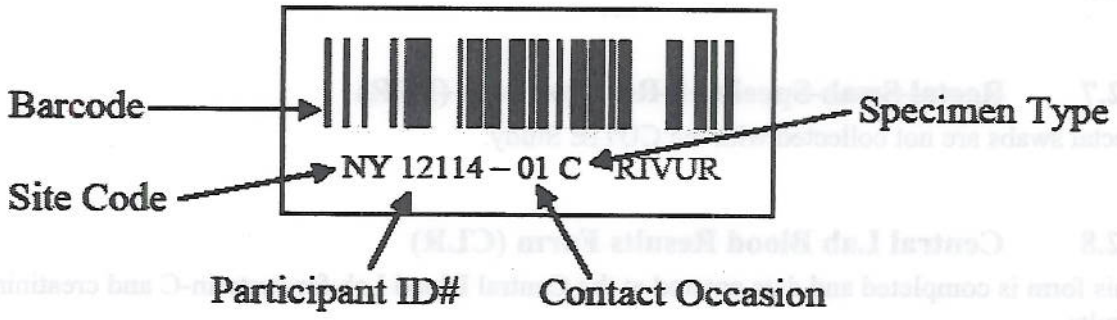
  Note: On the repository specimen labels, the participant ID number has been modified and begins with an NIDDK 3-field numeric site code, as shown in some of the example labels in Table 5.2 below. This replaces the usual 2-character CUTIE site code. The central labs use labels with the original CUTIE ID structure.

- Contact Occasion number

- Specimen type
  - U = Urine for biosample repository
  - C = Serum for Central Blood Lab (cystatin C and creatinine)
  - B = Blood in ACD tube(s) for genetics repository
  - S = Blood in SS tube for biosample repository

If no specimen type is indicated, this label is provided for use on shipping logs, or as an extra. If used to replace a label, please record the specimen type code using a permanent marker.

Diagram 5.1 Breakdown of a CUTIE Baseline specimen label



There are a maximum of 6 labels needed at the baseline (visit=01). If the participant is ≤ 20lbs, only 5 labels are needed at Baseline because Coordinators will collect only 1 ACD tube for the Genetics Repository (See Section 5.5.3. Blood Collection).

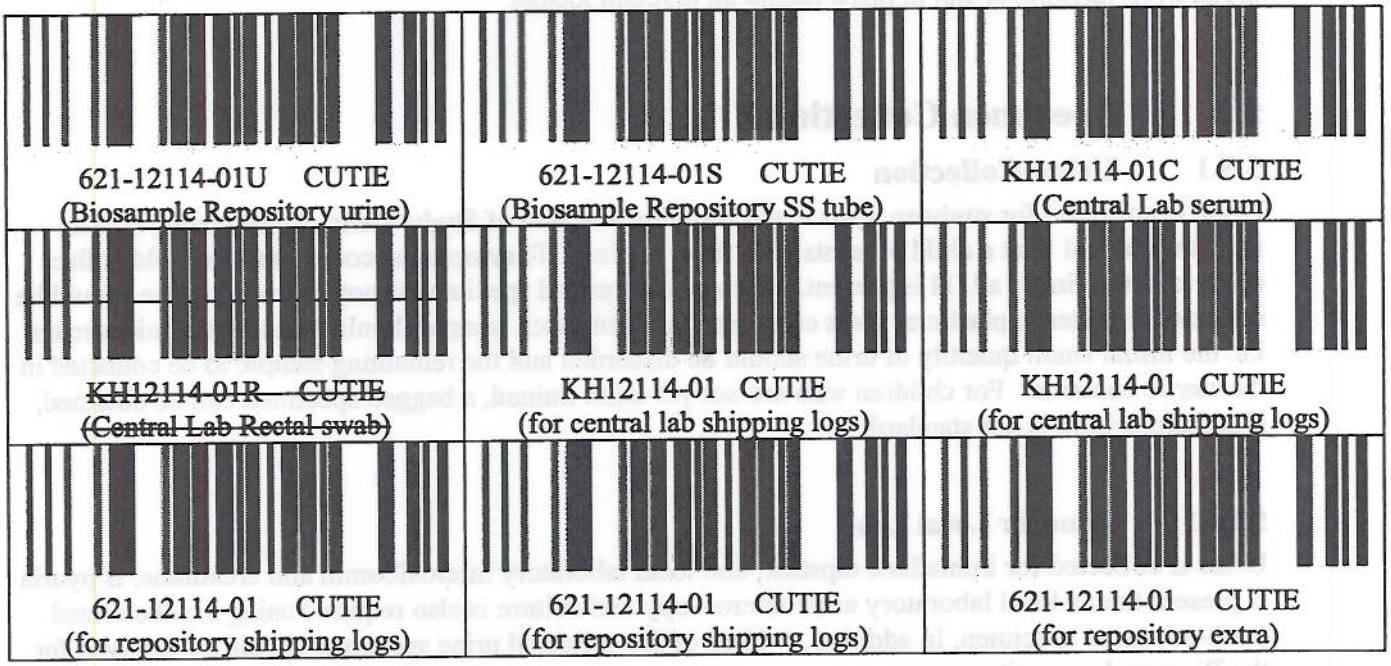
In addition, 4 extra labels have been included for each visit to use on shipping logs. These labels do not specify specimen type. If no specimen type is indicated, the label can be used as an extra or on paper shipping logs. If used in place of a specimen label, please record the specimen type code using a permanent marker.

It is critical that the correct labels are used on the specimens. To ensure appropriate labeling, coordinators and assisting personnel should become completely familiar with the codes being used. Table 5.2 shows sample specimen labels. The actual label is NOT identical to the table, so care should be used when choosing the correct label for the correct specimen.

Table 5.2 Sample specimen labels for study clinic in Philadelphia (CUTIE site code = KH, NIDDK site code = 621)

Baseline Labels

End-of-Study Labels



5.4 Specimen Storage at the Clinical Sites

The repository urine and repository blood specimens will be shipped fresh (not frozen), but may require refrigeration for a couple of hours prior to actual shipping, or overnight for specimens collected on non-shipping days. Please note: gel packs must be frozen prior to shipping to ensure refrigeration during transit. Processing and shipping instructions for each specimen type are detailed in section 5.5 below.

Serum shipped to the Blood Central Laboratory for cystatin-C and creatinine analysis will be shipped frozen in batches every 3rd month. These specimens must be frozen in an ultra-low freezer prior to shipping, see section 5.4.1.

5.4.1 Ultra-Low Freezer

The serum for cystatin-C and creatinine analysis must be stored at - 70° C. Frozen specimens must be stored upright in an appropriate ultra-low freezer. Each site Coordinator must make arrangements at their clinical site for this storage. An "appropriate" ultra-low freezer is a freezer that is monitored daily for temperature changes and control, has electrical power, alarm battery, and has major adverse events documented.

Each Study Coordinator must develop and document a clearly defined backup plan in the event of prolonged power and/or temperature failure to ensure the stability of the stored samples. Arrangements must be made such that the Coordinator is notified when an alarm is activated and there is a problem with the freezer. A specific alternative ultra low freezer must be identified (location and area documented) in the event that the specimens must be removed. The conditions in which specimens will be moved, who will move them, and the procedure for transport should be included, contact persons and phone numbers should also be documented in this plan. This plan needs to be developed and in place before an incident occurs.

5.5 Specimen Collection

5.5.1 Urine Collection

Urine is collected for study analysis at the Baseline and End of Study Visits. Additionally, if at an interim protocol visit a child presents with fever and/or UTI symptoms, coordinators should collect urine to determine if a UTI is present. When a catheterized specimen is not indicated, urine should be collected in a sterile plastic or glass container. A clean-catch sample should be collected mid-stream, i.e. the initial small quantity of urine should be discarded and the remaining sample to be collected in the sterile container. For children who are not yet toilet trained, a bagged specimen can be obtained, if catheterization is not standard.

5.5.1.1 Urine for Local Lab

Urine is collected for immediate dipstick, and local laboratory microalbumin and creatinine. If pyuria is present then a local laboratory urine microscopy and culture is also required using a catheterized (cath-ed) urine specimen. In addition, 4-10ml of the collected urine specimen should be reserved for the Biosample repository.

Urine specimens for local analysis should be delivered to the site's local laboratory within 1 hour of collection, or kept in a bag containing ice cubes or refrigerated until delivered. Urine remaining after local analysis should be transferred to the urine container provided by the Biosample repository. If a cath-ed specimen was obtained, Coordinator should use cath-ed urine for Biosample repository specimen. Once repository container is filled according to the laboratory procedure, tighten the cap on the container and store refrigerated until the shipper is ready to go.

5.5.1.2 Urine for Biosample Repository

Urine for Biosample Repository is collected at the Baseline and End-of-Study visits. The urine samples for the National Institutes of Health Biosample Repository at Fisher BioServices should be kept unfrozen, in the container provided by the Biospecimen Repository. A minimum of 4 mL, but up to 10 mL should be shipped if provided by the participant. If shipping more than an hour after collections, sample should be refrigerated until time of shipping.

The Biosample repository will provide collection and shipping kits including the urine collection container, an SS tube for repository serum collection (see section 5.5.3.4), packing and shipping materials, and pre-printed Federal Express labels for shipping of the samples. The collection container should be labeled with the participant ID label provided by the DCC, bar-coded and indicating specimen type 'U'. The Biosample repository sample collection kits will be shipped directly to each participating clinical site. To order more collection kits or shipping supplies, send an email to:
BIO-NIDDKRepository@thermofisher.com.

Full processing and shipping instructions for the Repository are provided in the document 'Instructions for Shipping Urine and Blood for the NIDDK BioSample Repository' (NIDDK-USL), see Appendix 5.2. This form is completed for both urine and blood shipments to the Biosample Repository. It also functions as the shipping log, and must be completed and included in the shipped package. Coordinators should keep a copy of all shipping forms on site. Data recorded on this form is not data entered into the DMS.

Shipments are to be made Monday through Thursday only – do not ship on Fridays. Specimens collected on Friday will have to be refrigerated over the weekend and shipped on Monday.

Send a shipment notification to the repository via email at BIO-NIDDKRepository@thermofisher.com or fax (301-515-4049) on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number in the notification. Contact the NIDDK Repository via email or call Heather Higgins (240-793-0353) or Sandra Ke (240-686-4702) regarding questions about packaging and shipping.

~~5.5.2 Rectal Swab Specimen~~

Rectal swabs are not collected with the CUTIE Study.

~~5.5.2.2 Procedures for Rectal Swab Collection and Shipping~~

Rectal swabs are not collected with the CUTIE Study.

5.5.3 Blood Collection

The blood collection protocol for CUTIE is dependent on each child's weight. The participant's weight determines the volume of blood that can be drawn. Diagram 5.2 shows the distribution of

blood collected among the local lab, central lab, and repositories at the baseline visit. Diagram 5.3 shows the End-of Study collection scheme. The collection scheme for End-of Study differs only in that no blood is collected for the Genetics Repository.

The priority for blood collection is as follows:

~~1. CBC (local analysis)~~

2. Blood serum for cystatin C and creatinine (central analysis)
3. Blood for the Genetic Repository
4. Blood for the Biosample Repository
5. Blood serum for electrolytes (local analysis)

Coordinators should meet and work with their local labs to discuss the blood collection protocol for CUTIE. Volumes approved for the study are very small and need to be drawn, distributed, and used very carefully. The labs will first insist they need more blood; however, these are the volumes that have been identified as workable by laboratory consultants on the study.

Diagram 5.2 Blood Collection Scheme for BASELINE VISIT

1.5ml in yellow SS tube, aliquot serum

2)

Priority 1: 0.5ml for **Cystatin C and Creatinine**
⇨ Batched & [redacted] at -70 , ship every 3 months to **Central Lab in Kansas City, MO** (C label

Priority 2 (collect if enough in *this* SS tube): 0.1ml serum for **Electrolytes**
⇨ Send to **Local Lab** (no label)

3)

For kids ≤ 20lb: collect ONE 3.0 ml ACD tube
For kids > 20lb: collect TWO 3.0 ml ACD tubes, $^2/_3$ full
⇨ Ship room temperature to **Genetics Repository** (B label)
If ACD tube(s) not collected at Baseline, then collect at a later clinic visit.

4)

Collect ONLY from kids >20lb
4.0ml in yellow SS tube ⇨ ***Spin*** and Ship unfrozen (with urine) to **Biosample Repository** (S label)

Diagram 5.3 Blood Collection Scheme for END-OF-STUDY Visit

2) 1.5ml in yellow SS tube, aliquot serum

Priority 1: 0.5ml for **Cystatin C** and **Creatinine**
⇨ Batched & FROZEN at -70 , ship every 3 months to **Central Lab in Kansas City, MO** (C label)

Priority 2 (collect if enough in *this* SS tube): 0.1ml serum for **Electrolytes**
⇨ Send to **Local Lab** (no label)

3) *Collect ONLY from kids >20lb*
4.0ml in yellow SS tube ⇨ ***Spin*** and Ship unfrozen (with urine) to **Biosample Repository** (S label)

5.5.3.1 Local Laboratory Blood

Blood is to be drawn for local electrolytes analysis at baseline and end-of-study.

Volumes are specified to assure enough blood is drawn to allocate to the central labs and repositories, within the total protocol specified allowance. The baseline and end-of study collection includes 1.5 mL collected in a serum separator tube, of which 0.1mL is analyzed locally for the electrolyte study and remaining 0.5 mL is shipped to the Central Blood Laboratory (Section 5.5.3.2). Note that not all electrolytes in a standard panel are included as study data, this might help to negotiate blood volumes (refer to the Blood Specimen Results Form, BSR). However it also might be cheaper to order the full panel, or preferred for clinical care, even though not all analytes are reported to the study.

Local specimens must be identified at each site in such as way that the local lab report can be easily linked to the participant study ID number. The DCC does not provide labels for specimens analyzed locally.

5.5.3.2 Central Blood Laboratory

The Central Blood Laboratory, located in Kansas City, Missouri, performs cystatin-C and creatinine studies on the frozen 0.5mL serum collected at baseline and end-of-study.

5.5.3.2.1 Equipment Needed

Participating sites are responsible for all collection and shipping supplies:

- 0.5mL Nalgene Cryogenic Vials, catalog number 5000-1012 from Nalge Nunc International 1-800-625-4327 (tubes will hold 1cc and are freezable).
- Participant specimen label provided by the DCC, specimen type 'C'
- Biohazard packaging, see Appendix 5.1 Pointers on Shipping Clinical Specimens
- Specimen tube tray
- Biohazard bag or Ziploc bag
- Cold paks

- Paper towels
- Styrofoam cooler for shipping
- Cardboard shipping box
- Dry ice for shipping
- Specimen Shipping Log

5.5.3.2.2 Instructions for specimen collection and shipping:

1. 0.5 mL of serum aliquot is needed, taken from a centrifuged serum separator tube.
2. The serum should be transferred to a dry Nalgene cryovial or another tube which can withstand - 70°.
3. The tube should be frozen at - 70° C. If there is to be delay in freezing at - 70° C, place in ice and keep refrigerated until the specimen can be frozen at -70° C.
4. The samples should be on dry ice and sent using overnight express on Monday or Tuesday only.
5. The serum samples can be sent in groups since we plan to batch the samples and run them in groups of 20.
6. The samples should be sent to:

The Nephrology Laboratory
The Children's Mercy Hospital
2401 Gillham Rd,
Kansas City, Mo. 64108
Attn: Nancy Wilson, ASCP

7. Be sure to include a CUTIE Central Lab Specimen Shipping Log (CSL)
8. When shipping, please call Nancy Wilson at 816-234-3013 or send an email to: nwilson@cmh.edu

5.5.3.3 Blood for Genetics Repository

Blood is collected at Baseline for DNA analysis (through cell line immortalization), and will be stored at the National Institutes of Health Genetics Initiative at the Rutgers University Cell and DNA Repository. If a sample for the Genetics Repository cannot be obtained at the baseline visit, it may be collected at a later clinic visit.

The repository will provide sample collection kits including the necessary ACD blood collection tubes, packing and shipping materials, and Federal Express labels for collection and shipping of the samples. Collection tubes should be labeled using the participant ID label provided by the DCC, bar-coded and noting specimen type 'B'.

Each collection kit should contain two 3 mL ACD tubes. One full tube should be collected on participants ≤ 20 lbs. Two tubes filled $^{2}/_{3}$ full should be collected from participants > 20 lbs (providing a total of 4 mL since ACD tubes do not come in 4mL sizes).

Shipping instructions for the Repository are provided in the document 'NIDDK Genetics Initiative Phlebotomy Form – CUTIE Study, study form code NIDDK-BSL. The NIDDK-BSL will also function as the shipping log, and must be completed and included in the shipped package. This form is not date entered into the study DMS.

The sample ID requested is the specimen ID from the specimen label, the alternate ID# is this same ID number.

Once collected, be sure to invert the tube gently 6 times to mix blood with additives and keep them at room temperature.

A shipment notification to the Genetics Repository on the day the FedEx shipment is required by email or fax. For complete instructions on packing and shipping samples to the Genetics Repository, please review the documents located behind the "NIDDK-BSL" tab in your MOP. Shipments are to be made Monday through Friday; the lab will receive specimens on Saturday.

The Repository must be notified when blood is shipped with the tracking number and specimen ID number. This can be done through the Web Portal at http://rucdr.rutgers.edu/shippingblood, by fax (1-732-445-1149), by phone (1-732-445-1498) or email witt@biology.rutgers.edu and peralta@biology.rutgers.edu. If Friday shipment, please indicate Saturday delivery.

5.5.3.4 Blood for Biosample Repository

Participants weighing more than 20 lbs, will also have 4mL blood collected for serum long-term storage at baseline and end-of-study. This blood is collected in a serum separator tube and shipped along with the urine specimen to the NIDDK Biosample Repository.

A 4mL serum separator (SS) tube will be included in the collection and shipping kit that Coordinator will receive from the Biosample Repository (also contains the urine specimen container mentioned in section 5.5.12). The SS tube should be labeled with the participant ID label provided by the DCC, bar-coded and indicating specimen type 'S'.

Each tube needs to be processed immediately following collection. The tube should be inverted 5 times to mix the clot activator with the blood. The blood should be allowed to clot vertically for 30 minutes, and then centrifuged at full speed for 10 minutes in swinghead units, or 15 minutes in fixed angle units. See Appendix 5.4 'How to Prepare a Quality Sample using vacutainer SST tubes'.

Packaging and shipping instructions for the Biosample Repository are provided in the document 'Instructions for Shipping Urine and Blood to the NIDDK Biosample Repository', study form code NIDDK-USL. The NIDDK-USL will also function as the shipping log, and must be completed and included in the shipped package. Coordinators should keep a copy of all shipping forms on site. Data recorded on this form is not data entered into the DMS.

Shipments are to be made Monday through Thursday only – do not ship on Fridays. Specimens collected on Friday will have to be refrigerated over the weekend and shipped on Monday.
Send a shipment notification to the repository via email at BIO-NIDDKRepository@thermofisher.com or fax (301-515-4049) on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number in the notification. Contact the NIDDK Repository via email or call Heather Higgins (240-793-0353) or Sandra Ke (240-686-4702) regarding questions about packaging and shipping.

5.5.3.5 Specimens for Quality Control

During the follow-up period of the study, sites will be asked and instructed on how to collect 'blind replicate' tubes/specimens for lab quality control monitoring. Such samples will be collected using the same collection and processing methods, but labeled with an alternate ID number (not the regular participant ID number). These replicates will be tested for quality control to check the precision of methods used by a laboratory analyzing blood, urine, and rectal swabs. No additional blood will be drawn on any one person, keeping the total volume collected within the limits specified in the protocol. Chapter 11, section 11.6.3 describes CUTIE's external laboratory QC procedures.

Appendix 5.1 – Packing and Shipping Instructions for NIDDK Genetics Repository, doubles as shipping log for genetics samples

NIDDK GENETICS INITIATIVE
PHLEBOTOMY FORM – RIVUR STUDY

SHIP AT ROOM TEMPERATURE IN SAFETY MAILER
ENCLOSE A COPY OF THIS FORM WITH BLOOD KIT

FOR RU LAB USE ONLY:

TO: DR. DOUGLAS FECKMAN/GENETICS
RUTGERS UNIV./CELL & DNA REPOSITORY
DIV. LIFE SCIENCES – NELSON LABS
604 ALLISON ROAD (RM. C120A)
PISCATAWAY, NJ 08854 8082

FAX: (732) 445-1149
PHONE: (732) 445-1498

WEB FORM:
http://rucdr.rutgers.edu/shippingblood

INITIAL: _____

PURPLE M.: _____

ID#: _____

FROM (NIDDK-RIVUR SITE): _____

SHIPMENT TO INCLUDE BLOOD SAMPLES FOR DNA/PLASMA

PURPLE TOP TUBES: ____
FOR WB DNA/PLASMA

NIDDK STAFF: PLACE TUBE LABEL HERE OR COMPLETE BY HAND
(VERIFY INFO AGAINST INFO ON BLOOD TUBES!!!)

SEX: M___ F___ AGE: _____

SAMPLE ID#: _____

ALTERNATE ID#: _____

TO BE COMPLETED AT COLLECTION SITE (BE SURE TO KEEP A COPY FOR YOUR FILES FOR DATA ENTRY):

DATE BLOOD DRAWN: ___-___-___ (MONTH–DAY–YEAR)

TIME DRAWN: _____ (24 HOURS)

FORM COMPLETED BY: _____

CONTACT THE RUTGERS CELL & DNA REPOSITORY TO CONVEY PACKAGE TRACKING NO./DATE OF SHIPMENT (SEE BELOW). IF BLOOD IS SHIPPED ON A FRIDAY FOR SATURDAY DELIVERY, CHECK FEDEX FORM FOR SATURDAY DELIVERY.

EMAILED/FAXED/
CALL IN BY*: _____ ___/___/___ _____
(SEE RUTGERS FAX/PHONE AS ABOVE) DATE TIME

PACKAGE TRACKING #: _____ _____ (CHECK SATURDAY DELIVERY ON DELIVERY FORM IF APPLICABLE)

TO BE COMPLETED BY RUTGERS UNIVERSITY CELL & DNA REPOSITORY
PRIOR NOTIFICATION REC'D: YES___ NO___ - IF YES, DATE/TIME ___/___/___ _____ AM/PM
CONFIRMATION OF RECEIPT OF BLOOD SAMPLE TO NIDDK SITE SENT BY: _____ DATE/TIME ___/___/___

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Appendix 5.1 – Packing and Shipping Instructions for NIDDK Genetics Repository, doubles as shipping log for genetics samples

CUTIE STUDY

FLOW SHEET FOR BLOOD SAMPLE COLLECTION

Yellow TOP TUBE FOR NIDDK GENETICS INITIATIVE at RUTGERS UNIVERSITY

1) Complete and attach I.D. labels to the tubes. **DO NOT write the patient's name or any other personal identification information (e.g. SS#, DOB) on the tubes.**

2) Collect blood specimen in the 1 yellow top tube with ACD. **Be sure to invert the tube gently 6 times to mix blood with additives and keep them at room temperature.**

3) Double check NIDDK CUTIE ID #, verify that ID information on tube matches that on the enclosed NIDDK-CUTIE Phlebotomy Collection Form.

4) Date and sign the NIDDK-CUTIE Phlebotomy Collection Form in the TO BE COMPLETED BY PHLEBOTOMIST section.

5) Package the blood tube in the safety mailer following the enclosed instructions. Be sure to seal the Styrofoam container with the red tape (water resistant).

6) Place the collection form (NIDDK-CUTIE Phlebotomy Collection Form) in the mailer box outside of the plastic bag. Tape cardboard box closed when assembly is complete.

7) Use the enclosed Fed Ex shipping label to ship the sample to the Rutgers University Cell Repository. Be sure shipping label is marked for priority overnight delivery.

8) For routine shipments be sure the outside of the box is labeled "Diagnostic Specimen Packed in Compliance with IATA Packing Instruction 650."

9) **Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339)**, and a courier will be dispatched to pick up the samples. **Be sure to give Fed Ex the Zip Code of the PICKUP address, not that of the destination.**

10) **Notify the Rutgers University Cell and DNA Repository** that blood is being shipped and provide the Federal Express tracking number(s) _____ and NIDDK-CUTIE ID #(s) _____. This can be done through the Web Portal at http://rucdr.rutgers.edu/shippingblood), by fax (1-732-445-1149),by phone (1-732-445-1498), or email witt@biology.rutgers.edu and peralta@biology.rutgers.edu

Appendix 5.1 – Packing and Shipping Instructions for NIDDK Genetics Repository, doubles as shipping log for genetics samples

ThermoSafe®
DiagnosticShipper

Assembly Instructions for ThermoSafe® Diagnostic Shipper Model 472 Transport Package for Diagnostic Specimens (in Conformance with Title 49 CFR, Part 173.199 and IATA Packing Instruction 650)

Read all instructions thoroughly before starting assembly

Required Components*:

- [illegible] – 6 Vacutainer® brand 10 ml specimen tubes with red rubber stoppers (Becton Dickinson No. 6530) or equal
- Scotch® brand ¾-inch wide reinforced packing tape (3M No. 898-24) or equivalent (not supplied)
- One expanded polystyrene foam mailer (body and lid)
- One 4¾-inch x 9-inch section of absorbent material
- Two 18-inch lengths of waterproof tape
- One press-lock plastic bag
- One corrugated mailing carton with locking tabs
- Two-inch wide package sealing tape (not supplied)

Assembly Procedure:

1. Cut two 5-inch long strips of ¾-inch wide reinforced packing tape (not supplied) to secure the rubber stopper of each filled specimen tube. Use the first strip of tape over the top of the rubber stopper and down along opposite sides of the tube. Use the second strip of tape to wrap around the specimen tube and also cover the cut ends of the first strip of tape (Fig. 1).
2. Place specimen tubes into the body of the foam mailer and cover the tubes with the absorbent material (Fig 2).
3. Place the lid of the foam mailer over the body and absorbent material (Fig. 2); and press the lid firmly until all sides of the lid meet the sides of the body.
4. Cut two 18-inch long strips of red, water-proof tape. Peel the white backing from the tape, and seal the foam mailer by completely covering the joint between the lid and the body (Fig. 3). The ends of the tape should overlap about an inch.
5. Place the sealed foam mailer into the press-lock bag, but do not seal the bag yet.
6. Slide the foam mailer and press lock bag into the corrugated mailing carton (Fig. 4). Use the space under the foam mailer to include the required itemized list of the mailer's contents.
7. Seal the press-lock bag, close the corrugated carton using the locking tabs, and use package sealing tape (not supplied) over the locking tabs.
8. The package must identify its contents as "Diagnostic Specimens" in type at least ¼-inch high. It also must display the diagnostic specimen marking: "UN3373" in type at least ¼-inch high inside a diamond measuring at least 2 inches by 2 inches whose line is at least 2 mm thick.

Fig. #1 Fig. #2 Fig. #3 Fig. #4

* Certification that this product meets United States and International Regulations governing the transport of diagnostic specimens is contingent on proper use of all "Required Components" as described in these instructions. Substitution or omission of supplied and required components, except as described here, is not permitted. Substitution of the supplied specimen tubes (primary receptacles) is permitted only when replacement primary receptacles have been shown to meet the requirements of Title 49 CFR, Section 173.199 and all applicable sections of the IATA Dangerous Goods Regulations, including but not limited to Packing Instruction 650; 5.0.2.9; 6.1.1; and 6.3.1.2.

SCA Packaging NA
ThermoSafe Brands
3930 Ventura Drive, Suite 450
Arlington Heights, IL 60004
www.thermosafe.com
800 323-7442 ◆ Fax 847-398-0643

SCA

Appendix 5.2 – Packing and Shipping Instructions for NIDDK BioSample Repository, doubles as shipping log for repository urine and serum samples

Instructions For Shipping RIVUR Urine and Blood to the NIDDK BioSample Repository

Sample ID: _____ - _____

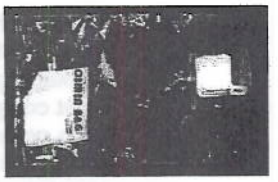
Urine collection date: _____/_____/_____ (mm/dd/yyyy)

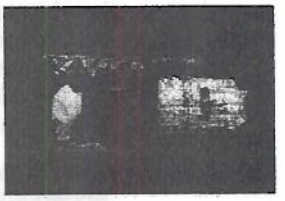
Blood collection date: _____/_____/_____ (mm/dd/yyyy)

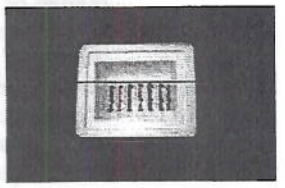
This package contains 10 ml of human urine and 4 ml of human blood (or less) for diagnostic purposes.

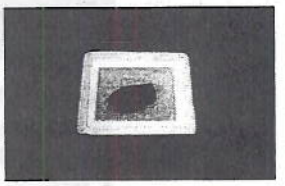
---

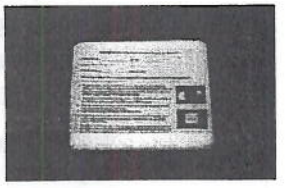
1. Freeze the gel pack included in the shipping kit prior to sample collection.
2. Enter the sample ID and date of collection for the urine and blood on the top of this form, on the urine cup and on the Vacutainer label. The sample ID is the participating site's three-digit NIDDK site ID, followed by the seven-digit participant ID. Please do not write any personal information on this form, the specimen containers, or anywhere on the box (e.g., patient name, SSN, address, phone number, etc.).
3. Collect the urine in the specimen cup and screw the lid on the cup. Verify that the lid is secured tightly, and wipe any urine off the outside of the container.
4. Place the urine cup and the white absorbent strip into the zip-lock bag. Seal the bag.
5. Insert the Vacutainer into the bubble wrap pouch. Place the pouch and the white absorbent strip into the zip-lock bag. Seal the bag.
6. Place the frozen ice pack in the bottom of the foam cooler.
7. Place the zip-lock bags containing the urine and blood on top of the ice pack. Make sure the urine container is in an upright position. Place bubble wrap around the urine to hold it in place.
8. Place the lid on the foam cooler. Fold and place this document on top of the foam lid (but under the cardboard box flaps). Close and seal the box with packing tape.
9. Affix the "UN 3373 Biological Substance Category B" label to the top of the box in the upper right corner. Affix the repository address label to the top of the box in the upper left corner.
10. Use the pre-printed FedEx air bill to ship specimens to the NIDDK Repository:
    a. Section 1, From: Fill in your name, return address, phone number and the date. Leave "Sender's FedEx Account Number" blank.
    b. Section 5, Packaging: Place a check mark in the "Other" box.
    c. Section 6, Special Handling: Place a check mark in the "No" box, indicating no dangerous goods are in the shipment.
    d. Section 7, Payment: Enter "1" under "Total Packages" and the total weight of the package.
    e. Follow the peel-and-stick instructions on the back of the air bill. As shown, affix the air bill to the side of the box.
11. Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339). Give them the account number (in Section 7, Payment) on the preprinted FedEx air bill and your pickup address. FedEx will dispatch a courier to pick up the package. Please schedule shipments Monday through Thursday. **The repository is closed on weekends, so do not ship specimens on Fridays.** Specimens may be refrigerated and shipped on the following Monday.
12. Send a shipment notification to the repository via email at BIO-NIDDKRepository@thermofisher.com or fax (301-515-4049) on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number in the notification.
13. Contact the NIDDK Repository via email or call Heather Higgins (240-793-0353) or Sandra Ke (240-686-4702) regarding questions about packaging and shipping.

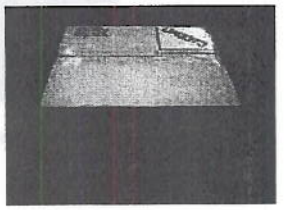












Revision date: 16 Apr 2007

Appendix 5.3 – Pointers on Shipping Clinical Specimens for Central Lab Shipping (FedEx)

At FedEx Express, we understand the importance of ensuring the safe shipping of clinical samples such as human or animal materials, including excreta, secreta, blood (including FDA-approved pharmaceuticals that are blood products), tissue and tissue fluids, as well as environmental test samples of soil and water. Our objective is to deliver these special shipments safely to their destinations in the same good condition as we receive them from you.

This brochure provides essential pointers to help you meet FedEx Express requirements on the proper packaging of these materials. In addition, all shipments must comply with all applicable local, state and federal laws governing packing, marking and labeling. Blood, urine, fluids and other specimens containing or suspected of containing infectious substances must be shipped according to applicable government and International Air Transport Association (IATA) regulations. For more information, call 1.800.GoFedEx 1.800.463.3339 and press "81" to reach the Dangerous Goods/Hazardous Materials Hotline.

The illustrations depict sample packaging that is acceptable for shipping clinical samples such as human or animal materials, including excreta, secreta, blood (including FDA-approved pharmaceuticals that are blood products), tissue and tissue fluids, as well as environmental test samples of soil and water. All of the packaging illustrated here are acceptable and may be used in any combination as long as the four basic requirements for acceptable packaging are met.

NOTE: Specific requirements for Diagnostic Specimens are highlighted and underlined below.*

GENERAL ACCEPTABLE PACKAGING

Proper packaging of clinical samples and environmental test samples includes four basic requirements:

1. Watertight Primary Receptacles
2. Watertight Secondary Receptacles
3. Absorbent Material
4. Sturdy Outer Packaging

NOTE: Internal filler or cushioning is recommended to protect fragile contents and limit movement.

For Diagnostic Specimens containing liquids, absorbent material is required between the primary and secondary receptacles. For both liquids and solids, cushioning material is required.

*Dangerous-goods regulations can be reviewed in the IATA Packing Instruction 650.

1. Watertight Primary Receptacles

All primary receptacles must have positive closures (such as screw-on, snap-on or push-on lids) that must be taped.

For Diagnostic Specimens, primary receptacles may be glass, metal or plastic. Positive means of ensuring a leak-proof seal, skirted stopper or metal crimp seal must be provided. Reinforce screw caps with adhesive tape.

For liquid specimens, the primary receptacle(s) must be leak-proof and must not contain more than 1 L.

The primary or secondary receptacle(s) must be able to withstand, without leakage, an internal pressure producing a pressure differential of not less than 95 kPa in the range of -40 C to 55 C (-40 F to 130 F).

For solid specimens, the primary receptacle(s) must be siftproof and not contain more than 500 g.

Plastic Canister

Glass/Plastic Jar

Glass/Pla Vial

2. Watertight Secondary Receptacles

To prevent contact between multiple fragile primary receptacles, individually wrap or separate each and place inside a leak-proof secondary receptacle.

For Diagnostic Specimens, enclose an itemized list of contents between the secondary packaging and the outer packaging. For solids, the secondary packaging must be siftproof. These illustrations below are not intended to represent secondary containers for Diagnostic Specimens. Secondary containers for Diagnostic Specimens must be certified by the manufacturer prior to use.

Sealed Styrofoam® Container (1-inch-thick minimum)

Sealed Plastic Bag

Plastic Canister

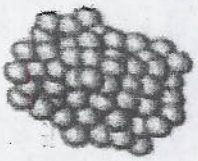
Screw-Cap Can

Appendix 5.3 – Pointers on Shipping Clinical Specimens for Central Lab Shipping (FedEx)

3. Absorbent Material

Place absorbent material between the primary and secondary receptacle, making sure that multiple primary receptacles are individually wrapped to prevent contact. Use enough absorbent material to absorb the entire contents of all primary receptacles.

Cellulose Wadding



Cotton Balls

Super-Absorbent Packet

Paper Towels

4. Sturdy Outer Packaging

Sturdy outer packaging must be rigid, consisting of corrugated fiberboard, wood, metal or rigid plastic and be appropriately sized for content.

For liquids, the outer packaging must not contain more than 4 L.

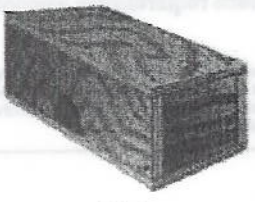
For solids, the outer packaging must not contain more than 4 kg.

When using an airbill pouch on outer packaging, the minimum package size that FedEx Express will accept is 7" x 4" x 2". For outer packaging smaller than these dimensions, use a plastic FedEx® Clinical Pak as an overwrap. As long as the final package meets the four basic packaging requirements, you may insert your package into the FedEx Clinical Pak to comply with the minimum acceptable size. (See "FedEx Clinical Pak" on the following page.)

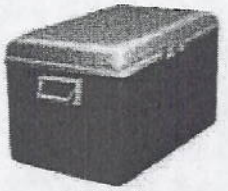
For Diagnostic Specimens, the minimum outer-container size in the smallest overall external dimension is 4 inches.

Each completed package must be capable of withstanding a 4-foot (1.2-meter) drop test outlined in IATA 6.6.1. The outer package must be rigid.

Corrugated Fiberboard



Wood



Rigid Cooler

Rigid Plastic Container

MARKINGS: Patient specimens for which there is minimal likelihood that pathogens are present are marked by the shipper "Exempt human specimen" or "Exempt animal specimen" as appropriate to comply with current IATA regulations. Each UN3373 shipment must show the text: "BIOLOGICAL SUBSTANCE, CATEGORY B", "DIAGNOSTIC SPECIMENS" or "CLINICAL SPECIMENS" at least 6 mm high, marked on the outer package adjacent to the following diamond-shaped mark.

The UN mark must be in the form of a square set at an angle of 45 degrees with each side having a length of at least 50 mm (2 inches). The width of the line must be at least 2 mm and the letters and numbers must be at least 6 mm high.

The name, address and telephone number of a responsible person must be marked on the package **OR** provided on the airbill.

Finally, if more than one properly prepared Diagnostic Specimen shipment is placed into another outer package, this constitutes an overpack. The word "OVERPACK" must be marked on the outer package and all other required package markings must be reproduced on the outside of the overpack.

Specific requirements:
Please consult the current ICAO/IATA regulations handbook for specific requirements for the following:

a. Diagnostic Specimens shipped refrigerated or frozen.
b. Diagnostic Specimens shipped in liquid nitrogen.

AIRBILL ENTRIES

If a paper airbill is used, the following text must be included: "Biological Substance Category B", "Diagnostic Specimens" or "Clinical Specimens" and "UN 3373". If not marked on the outer package, the name, address and telephone number of a responsible person must be marked on the airbill.

Appendix 5.3 – Pointers on Shipping Clinical Specimens for Central Lab Shipping (FedEx)

Don't Forget

Infectious substances or probable infectious substances require additional specifications and must be shipped according to applicable government and IATA requirements.

Shipments marked or labeled 6.2 (infectious materials) and/or containing dry ice cannot be shipped inside the FedEx Clinical Pak.

Consult the Occupational Safety and Health Administration (OSHA) regulations to determine if your commodity requires the biohazard label.

FedEx Express will not accept clinical samples, Diagnostic Specimens or environmental test samples packaged in the FedEx Envelope, FedEx Tube, FedEx Pak or any FedEx box.

- Don't place clinical samples, Diagnostic Specimens (UN3373) or environmental test samples in a FedEx Express Drop Box. Please call FedEx for pickup, or you can drop off the shipment at any staffed FedEx location or FedEx Authorized ShipCenter. FedEx Kinko's Office and Print Centers may accept FedEx Clinical Pak shipments provided they do not contain UN3373. For further assistance call 1.800.GoFedEx 1.800.463.3339.

- Mark and weigh packages correctly.
- Have packages ready when you call for pickup.

NOTICE

FedEx Express will refuse to accept packages not meeting FedEx Express, government or IATA requirements.

This brochure is in no way intended to replace requirements mandated by 49CFR and IATA. This is for informational purposes only.

This packaging brochure is provided free to FedEx Express customers to reduce the possibility of loss or damage during transit. It is NOT intended to be a comprehensive guide for packaging items we accept for transit. We make no warranties, expressed or implied, regarding this information. Proper packaging is the sole responsibility of the shipper. For more information and comprehensive guidelines, contact the FedEx Dangerous Goods/Hazardous Materials Hotline at 1.800.GoFedEx 1.800.463.3339, and press "81." Refer to the current FedEx Service Guide for terms, conditions and limitations applicable to FedEx® delivery services.

Styrofoam® is a registered trademark of Dow Chemical Company.

Appendix 5.4 – How to Prepare a Quality Sample Using Vacutainer™ ™ SST Tubes

BD Indispensable to human health

How to Prepare a Quality Sample

Using BD Vacutainer™ SST™ Tubes

Invert
5
Times

- Gently invert 5 times to mix clot activator with blood.

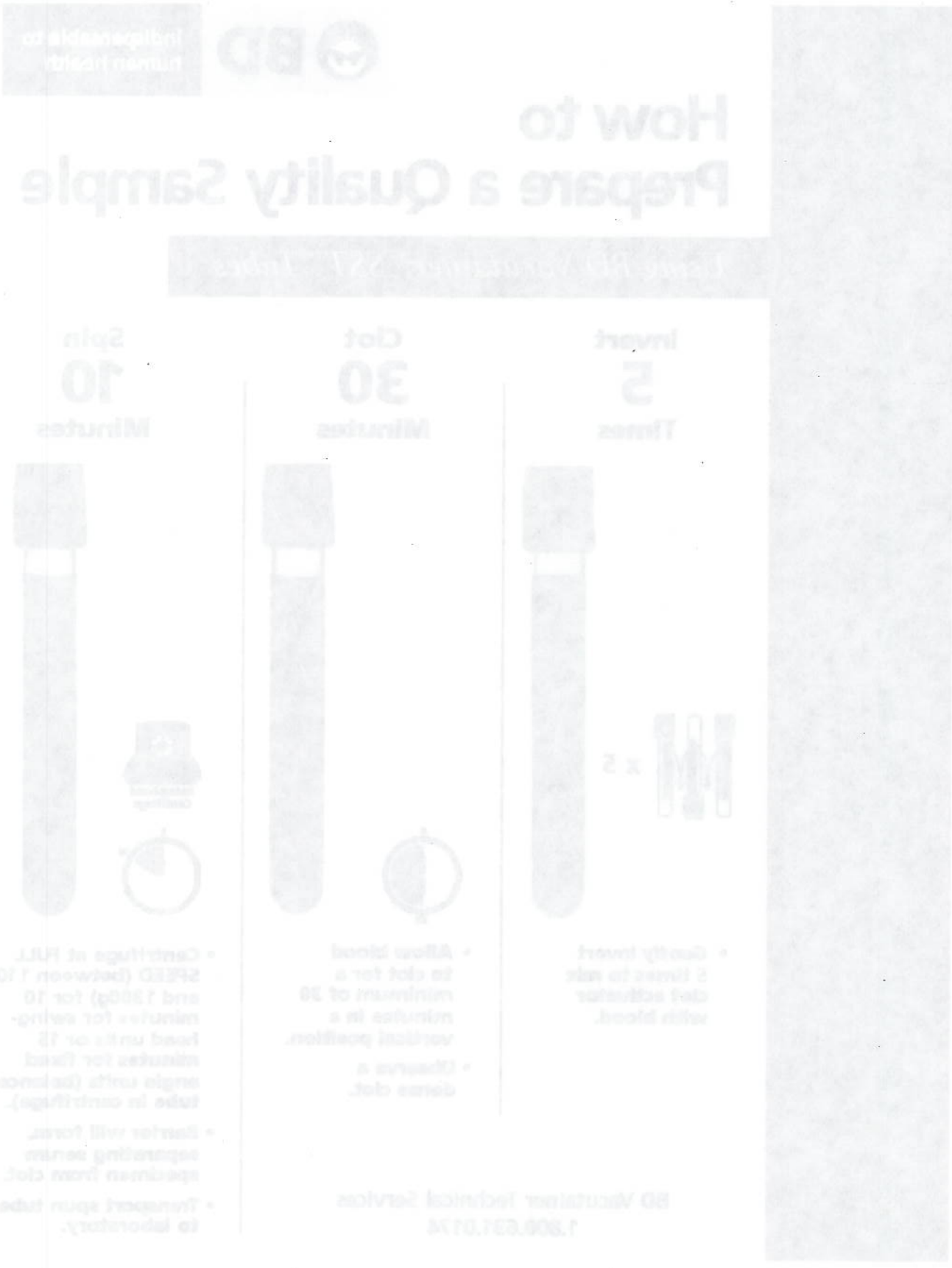
Clot
30
Minutes

- Allow blood to clot for a minimum of 30 minutes in a vertical position.
- Observe a dense clot.

Spin
10
Minutes

- Centrifuge at FULL SPEED (between 1100 and 1300g) for 10 minutes for swing-head units or 15 minutes for fixed angle units (balance tube in centrifuge).
- Barrier will form, separating serum specimen from clot.
- Transport spun tube to laboratory.

BD Vacutainer Technical Services
1.800.631.0174



Chapter 7: Follow-Up Contacts

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Chapter 7: Follow-Up Contacts

7.1 Overview

During the two-year follow-up period, parents will be contacted by phone every 2 months and scheduled for clinic visits every six months. Follow-up contacts and visits will continue through 24 months..

In brief, the follow-up contacts will provide monitoring for participant safety, as well as data for endpoint ascertainment. They are designed to insure that the study captures data on all potential urinary tract infections (UTIs) that occur during the 24 months of study. At each follow up contact, Coordinators will collect data on the occurrence of any adverse events and medical care visits, review concomitant medication use, and obtain the history of urine and bowel toilet training since the last study contact.

Parents/guardians will be asked to keep a patient diary recording occurrences of illness, medical care visits, and newly prescribed concomitant medications. This diary will be reviewed during all telephone and clinic visit follow-up contacts.

7.2 Scheduling of Follow-up Contacts

Follow-up procedures will continue for each participant until their end-of-study visit at 24 months after enrollment, regardless of designation of treatment failure.

Project Coordinators should always remind parents/guardians that routine follow-up consists of both clinic visits and interim telephone interviews, which are scheduled every 2 months. At the enrollment and baseline visit, the Coordinator should schedule the next two telephone contacts, at 2 and 4 months from enrollment. At the end of every follow-up contact, the next 2 contacts should be confirmed or scheduled with the parent/guardian.

When scheduling clinic visits, the Coordinator will always need to verify that the principal investigator or his/her designee (which may be the Coordinator) is available to perform any necessary examinations during scheduled contacts.

7.2.1 Target Dates and Contact Windows

Target contact dates occur exactly every 2 calendar months from a participant's date of enrollment, and continue through the end of the 24-month study period. All protocol scheduled follow-up contacts should be scheduled on, or within ± 10 days, of a target date. This allows a 21-day window for Coordinators and parents to work with when scheduling follow-up contacts.

Table 7.1 below shows the first three target dates and resulting contact windows for a patient enrolled January 1, 2007.

Table 7.1
Target Dates and Contact Windows for a Patient Enrolled January 1, 2007

Study Contact Occasion	Target Date	Window (± 10 of target date)
02 (2-mo phone contact)	March 1, 2007	Feb 19 – Mar 11
03 (4-mo phone contact)	May 1, 2007	Apr 21 – May 11
04 (6-mo clinic visit contact)	July 1, 2007	Jun 21 – Jul 11

It is important to remember that target dates are **always scheduled from the date of enrollment,** regardless of the last contact date. The CUTIE DMS contains a CUTIE Participant Follow-up Schedule Report that can be run on each patient, listing the target contact date and the upper and lower dates of the window for the full 24 months of the participants study. A copy of this report should first be provided to the parent/guardian at the time of enrollment, and the information may also be written into the patient handbook/diary.

7.2.2 How closely together can two contacts be scheduled?

The Coordinator should make every effort to schedule protocol contacts within the contact windows for the participant's target dates. However, there may be instances when this is not possible. Protocol contacts can be scheduled outside of the target date window if necessary. The CUTIE DCC would rather have data outside the time period than no data at all, but it would be a waste of resources to schedule two contacts too close together.

The general rule of thumb is that scheduled contacts for enrolled participants must be at least 30 days apart. When a participant contact (clinic visit or phone) cannot be scheduled prior to 30 days before the next required contact, then it must be considered skipped (i.e., there will be no data collected for this contact occasion). If a contact is skipped, an FUP form for that expected visit must still be completed and entered in the DMS. Section A of the FUP form (Contact Information) will allow Coordinators to specify that the contact occasion was missed.

7.2.3 Follow-up Clinic Visits and Reminders

Since the clinic visits allow Coordinators to gather more information than the telephone contacts, it is especially important that study clinic visits not be skipped. If a study clinic visit is skipped, the next contact, which would normally be a follow-up phone contact, should be scheduled as a clinic visit replacing the scheduled telephone contact.

Postcard Reminders

Two to three weeks before a follow-up clinic visit, the Coordinator should send a postcard reminder to the participant and his/her parents. On the postcard, the Coordinator should remind the parent/guardian to bring in the Participant Handbook/Diary and any current medicines the child is taking.

Phone Call Reminders

Coordinators should also follow-up with a phone call reminder two to three days before each follow-up clinic visit. Again, the Coordinator should remind the parent/guardian to bring in the handbook/diary and any current medicines the child is taking.

7.3 Follow-up Data Collection Forms

The Tables below summarize the data collection forms used during participant follow-up in the CUTIE study. Some forms must be completed at specific clinic contacts. Others are completed or updated on an 'as needed' basis. These forms are often triggered by data collected or responses given during the required data collection, or are based on the participant's status in the study at a particular time. Table 7.2 lists both the administrative forms that Coordinators must maintain and keep updated, as well as the forms that are to be completed on an as-needed basis throughout the duration of the study. Table 7.3 lists the forms that are required at specific study contacts. Scheduled follow-up contacts in clinic or by telephone require certain forms such as the Follow-up Contact Form (FUP), and verification of contact information on the Participant Contact Form (PCF).

There are forms which are completed on an as-needed basis, in addition to being required at specific study contacts.

Table 7.2 Data Collection Forms completed or updated on an as-needed basis

Informed Consent Tracking Form (ICT) Participant Contact Form (PCF) Record of Contacts Form (RCF) VCUG Sedation Form (VSF) VCUG/Ultrasound Scans Shipping Form (VUS)	Adverse Events Form (AEF) Urine Specimen Results Form (USR) Medical Care Notification From (MCN) Medical Care Abstraction Form (MCA) DMSA Scan Shipping Form (DSS) DMSA Sedation Form (DSF)

Table 7.3 Summary of Data Collection during Scheduled Follow-up Contacts

DATA COLLECTION FORMS	2-mo Tele	4-mo Tele	6-mo Clinic	8-mo Tele	10-mo Tele	12-mo Clinic	14-mo Tele	16-mo Tele	18-mo Clinic	20-mo Tele	22-mo Tele	24-mo Clinic
Contact Occasion	02	03	04	05	06	07	08	09	10	11	12	13
Follow-Up Contact Form (FUP)	X	X	X	X	X	X	X	X	X	X	X	X
Participant Contact Form (PCF)	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Form (CMF)	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam Form (PEF)			X			X			X			X
LIA Questionnaire (LIQ)						X						X
DV Questionnaire (DVQ)						X						X
DES Treatment Form (DTF)*						X						X
DMSA Results Form (DMF)*						X						X
DMSA Sedation Form (DSF)*						X						X
DMSA Scans Shipping Log (DSL)*						X						X
Ultrasound Scans Shipping Log (US)*												X
Urine Specimen Results Form (USR)*												X
Specimen Collection Form (SCF)												X
Blood Results Form (BSR)						X						X
Central Lab Shipping Log (CSL)						X						X
NIDDK Urine and Blood Shipping Log (NIDDK-USL)												X
NIDDK Genetics Blood Shipping Log (NIDDK-BSL)												X
NIDDK Urine and Blood Shipping Log (NIDDK-USL)												X
NIDDK Genetics Blood Shipping Log (NIDDK-BSL)												X

*also completed as need throughout the study

7.4 Detailed Follow-up Procedures

7.4.1 DMS Participant Follow-up Summary Report

The DMS will include a report that the Coordinator can run prior to a participant's follow-up contact. This report will summarize data collected during previous contacts that will be helpful to the Coordinator during the contact interview. Reported information will include such things as whether the participant is classified as a treatment failure, a summary of previous follow-up contact compliance, previous adverse event reporting, and concomitant medication. It is important to note, that a patient's Follow-up Summary Report will only be current if all previous data entry and query resolutions have been completed for that patient.

7.4.2 Participant Handbook/Diary

At baseline, each participant's parent/guardian will be given a participant handbook/diary, and a follow-up schedule. The handbook provides a summary of procedures associated with the follow-up contacts. The handbook also functions as a diary for recording any fever or illnesses, medical care visits, and changes in concomitant medications that need to be reported to the Coordinator at each follow-up contact. Other important information and instructions are also documented in the handbook.

7.4.3 Participant Record of Contacts Form (RCF)

The RCF is used to document every attempt to contact a participant's parent/guardian in order to schedule a study contact. In addition, contacts made to the clinics initiated by the parent/guardian to reschedule contacts, or to report illness or medical care visits should also be documented in the RCF. Protocol scheduled contacts should not be reported on the RCF.

Refer to the RCF QxQ's for specific item-by-item instructions.

7.4.4 Protocol Scheduled Clinic Follow-up Visits Data Collection

A summary of required data collected during the protocol scheduled follow-up contacts is provided in Table 7.3 above. The follow-up clinic visits focus on adverse events, concomitant medication use, and the status of the child's toilet training.

7.4.4.1 Modification of Informed Consent

A participant may modify their Informed Consent at any time during the follow-up period. If a participant indicates a change in their consent to participate in the study, complete an Informed Consent Tracking Form (ICT).

7.4.4.2 Physical Exam (PEF)

Each protocol scheduled clinic visit includes a brief physical exam. The exam includes temperature, blood pressure, and height and weight measures, as well as a brief abdominal exam. The physical exam should be performed at the beginning of the clinic visit, prior to completion of the FUP and CMF forms. Any abdominal tenderness, or other medical

conditions or complaints discovered during the physical exam are collected according to instructions on the FUP.

7.4.4.3 Protocol Scheduled Follow-Up Form (FUP)

The FUP is the primary instrument used during a follow-up contact. The form will provide instruction about additional data collection and forms if needed, based on responses to specific questions. The FUP form is only used during protocol scheduled contacts with participants.

Questions related to side effects, adverse events, and medical care received since the last contact will trigger the AEF and the endpoint data collection forms MCN and MCA. Refer to Chapter 9: Participant Safety and Adverse Event Reporting for data collection procedures, and the AEF QxQ for question by question instructions. Refer to Chapter 10: Medical Care Abstraction and Endpoints for data collection procedures on the MCN and MCA forms, as well as the QxQ for each form.

Concomitant medication use is also queried on the FUP, but details should be collected on the CMF.

The FUP also includes questions related to interim voiding and bowel history, and age at toilet training.

Refer to the FUP QxQ for additional information.

7.4.4.4 Specimen Collection at Clinic Visits (SCF, BSR)

Blood and urine specimens are collected from patients at baseline and the 24 month follow-up visit.

7.4.5 The 12 Month Clinic Follow-up Visit

The only differences between the 12 month follow-up clinic visit and other follow-up clinic visits (not including the end-of-study visit Section 7.4.6) are:

- All normal follow up forms including the FUP and CMF should be completed. If the child has received any medical care this should also be documented in the appropriate fashion.
- The self administered questionnaires, LIA Questionnaire (LIQ) and DV Questionnaire (DVQ) are administered. Refer to chapter 4: Enrollment and Baseline, section 4.5.3.

Participants who have a study endpoint (as determined by the Endpoints Committee) prior to the 12 month follow-visit, will have different scheduling criteria for their repeat DMSA. In this situation, the DCC will provide important information regarding any scheduling of repeat DMSA scans. All other data collection procedures for the 12 month clinic follow-up visit should proceed as documented above.

7.4.5.1 Scheduling the 12 month DMSA

A DMSA scan will only be performed at 1 year if there is an interim febrile UTI.

7.4.6 The End-of Study Follow-up Clinic Visit

Follow-up procedures continue for a two-year period after enrollment, regardless of whether or not potential endpoints occur,, or the participant is deemed a treatment failure.

The end-of-study follow-up clinic visit should take place during the 24th month of follow-up (contact occasion 13). Concerted effort should be made to obtain the required clinic data regardless of how well a participant's previous participation has been, including those participants who are on telephone contact only, and including participants who have dropped out of the study. Without complete assessment of study endpoints, the scientific validity of the entire study may be compromised.

The end-of-study visit includes the same procedures described above (section 7.4.4) for follow-up clinic visits, but also includes:

- DMSA scans, assessing new or worsening renal scarring. Refer to Chapter 3: Radiology.
- The self administered questionnaires, LIA Questionnaire (LIQ) and DV Questionnaire (DVQ) are administered. Refer to chapter 4: Enrollment and Baseline, section 4.5.3.
- Blood and urine collection. Refer to Chapter 5: Specimen Collection and Processing.

Refer to Table 7.3 for the required data collection forms at this visit.

If a participant has been on telephone-contact-only, special efforts should be made to try and get the participant and parent/guardian in for this last clinic visit. If the participant has previously dropped out of the study, but has not refused consent, a final effort should be made to have the participant and parent/guardian come in for this exit clinic visit.

At the final routine clinic visit the participant and their family will be given a certificate of appreciation or a commemorative token for his or her 2-year commitment to the CUTIE study.

7.4.6.1 Scheduling the End-of-Study DMSA

The 24 month DMSA scan should be scheduled and obtained within the 20 day window, prior to the 24 month clinic visit, while participants are still on study medication. The clinic visit should be rescheduled if the images are not obtained. However all scheduling should be done within the protocol scheduled window.

Participants who have a study endpoint (as determined by the Endpoints Committee), may have different criteria for their radiology scans. Refer to Chapter: 3 Radiology for specific

instructions on scheduling DMSAs for these participants. In this situation, the DCC will provide important information regarding any scheduling of repeat DMSA scans.

Refer to Chapter 3: Radiology for detailed instructions on study procedures for data collection.

7.4.6.2 Specimen Collection

Specimen collection procedures at the end-of-study clinic visit are similar to collection at baseline, including urine and blood collection. The exception being that blood is collected for plasma storage at the NIDDK BioSample repository, rather than DNA. It is also expected that most of the participants who were less than 20lbs at baseline will now be over 20 lbs, doubling their blood collection to 10mL total.

Refer to the detailed procedures on specimen collection, processing, and shipping documented in Chapter 5: Specimen Collection.

7.4.7 Telephone Follow-up Contacts

Parents will be scheduled for a telephone interview every 2 months after their child's enrollment, between the clinic follow-up visits, until the conclusion of the study. The Study Coordinator will send a reminder postcard to the participant two weeks before the scheduled telephone interview. If that scheduled date and time is not convenient, the Coordinator requests a phone call from the participant to reschedule the telephone interview.

Prior to making the telephone call, the DMS follow-up report should be reviewed. At the prearranged time, the Study Coordinator calls the participant and conducts the interview. During the interview, the Coordinator should ask the parent if they have any information recorded on the patient handbook/diary that is important. The interview consists of administering the Follow-up Contact Form and associated forms (FUP, Section 7.4.4.3) and updating the participant information on the PCF. Refer to Section 7.4.4.3 regarding administration of the FUP and associated forms.

Upon completion of the telephone follow-up contact, the date of the next follow-up contact should be confirmed, and a date for the second following contact should be scheduled.

7.5 Alert Notifications

Clinically significant findings (laboratory, or examination) in a participant during the study follow-up would require reporting on the Adverse Event Form (AEF), regardless of whether this is reported on data collection forms as study data or not. An example would include: laboratory analysis that may be done locally as clinical care, or even because requesting a panel from the lab is more efficient.

In addition, clinical sites have a responsibility to report these finding to a participant's primary care providers. This reporting is handled by each site's Investigator.

7.6 Non-Protocol Sick Child Clinic Telephone Calls and Visits

In the event of inter-current illness involving fever or symptoms related to a urinary tract infection, parents/guardians will be instructed to (1) contact primary care providers and study personnel, (2) have their child evaluated within 24-48 hours, and (3) have a urine specimen obtained to evaluate for the presence of UTI.

Sick child clinic calls and visits that are outside of a patient's target date contact window are not considered protocol follow-up contacts, and do not include the standard follow-up data collection (i.e. FUP). Telephone calls reporting an illness are to be documented on the PCF.

If a sick participant is scheduled and seen in clinic for a sick visit, all the appropriate AEF, MCN and MCA data collection should occur. If the participant is referred elsewhere for medical care, the parent should be instructed to update the participant handbook/diary to document fever and symptoms, the medical care visit, and any new medication prescriptions. The Coordinator should also make arrangements with the parent to follow-up on the event, and to complete the required study data collection and reporting.

Refer to Chapter 9: Participant Safety and Adverse Event Reporting and the AEF QxQ for data collection procedures on adverse events. Refer to Chapter 10: Medical Care Abstraction and Endpoints and the MCN and MCA QxQ's for data collection procedures of a sick medical care visit or a medical care visit reported.

If an on-site sick visit (that is, a sick visit to a CUTIE Study clinic) occurs within a patient's target date contact window, then the Coordinator should try to go ahead and collect the follow-up contact data as specified in section 7.4 of this chapter. This would replace any previously-scheduled protocol contact within that contact window, and prevent the patient's family from having to come back to clinic for a study protocol visit.

7.7 Use of Proxy

During the course of the study, it may be necessary to use a 'proxy' instead of the participant's parent/guardian who typically responds to the study interviews. For example, if the participant's parent or guardian that normally provides the study data becomes extremely ill, incompetent, dies, or is no longer the participant's caregiver or living in the home, rendering them unable to respond to interview questions, a proxy should be used. A "proxy" would be someone who responds on behalf of the participant's parent/guardian who typically has provided the study data. The proxy must be someone very close to the participant, such as a relative, caretaker, or friend, who is in frequent (e.g., daily) direct contact with the participant.

The Participant Contact Form completed at the baseline visit, and updated throughout the study should include proxy (or next of kin) contact information. This contact information may also be helpful when it is difficult to reach the parent or guardian in general.

7.8 Changes in Clinic Follow-up Procedures

The FUP form begins with a short section for documenting contact information related to the specific follow-up contact, and any change in protocol procedures for this contact.

7.8.1 Telephone Contact Replaces Clinic Visit

If a participant and their parent/guardian is unable to attend clinic visits due to severe health problems, geographical relocation, or another reason, but agrees to respond to the CUTIE telephone interview, this information must be indicated on the FUP. This will inform the DCC that follow-up is continuing, but data forms relating to a clinic visit will not be forthcoming for this contact occasion.

If at a later point in time the participant is able to resume clinic visits, record this appropriately on the FUP completed at the clinic visit either by indicating a regularly scheduled clinic visit or a clinic visit replacing a telephone contact.

7.8.2 Clinic Visit Replaces Telephone Contact

Occasionally, it may be appropriate to replace a telephone contact with a clinic visit, for example if a participant has missed a previous clinic visit but is now available for a visit. However, each protocol scheduled clinic visit (6, 12, 18, and 24 months) should still be expected, even if clinic visit occurred two months prior.

All scheduled follow-up clinic visits follow the same data collection procedures for the clinic visit in this situation, the usual follow-up clinic visit forms should be administered. Indicate that a clinic visit is replacing the telephone contact on the FUP so the DCC will know what forms are expected for this contact occasion.

7.9 Changes in Participants Follow-up Status

7.9.1 Participant or Parent/Guardian Refuses to Come to Clinic

If a participant and parent/guardian are not willing to come to the clinic then the Coordinator should only conduct telephone follow-up contacts. If the parent/guardian who typically provides interview responses is not willing or unable to continue in telephone contacts then the Coordinator should arrange to contact another family member or caregiver who can supply reliable data. This would need to be a person who has regular contact with the participant and is continually aware of their medical status.

7.9.2 Early Study Endpoint Participants

Participants who have had a study endpoint assessed by the Endpoints Committee will follow a different schedule for repeat DMSA imaging. The DCC will provide a report that notifies the Coordinator and Investigator of any endpoint determinations of treatment failure, and will provide instruction on the DMSA scheduling as specified in the protocol.

7.9.3 Participant is Deceased

This is a serious adverse event and data must be collected on an AEF as well as any other study forms that may be required or triggered, (i.e. FDA3500A, SAE, MCN, MCA).

When the clinical center staff becomes aware that a participant is deceased, an FUP for the next contact occasion should be completed, even if the target window for that contact is not yet open. The type of contact is "missed" with the reason being that the participant is deceased. Adverse event reporting and corresponding medical care forms need to be completed.

Refer to Chapter 9: Participant Safety and Adverse Event Reporting and the AEF QxQ for data collection procedures on adverse events. Refer to Chapter 10: Medical Care Abstraction and Endpoints and the MCN and MCA QxQs for data collection procedures.

7.9.4 Participant has Moved Away

The participant has moved away and the participant and parent/guardian cannot or will not return for follow-up appointments and any scheduled follow-up visits. If the participant has moved close to another CUTIE clinical center area, the participant may be transferred to the other CUTIE clinic. The DCC should be contacted for instructions on how to transfer participant from one center to another. The Transfer of Participant Form (TRN) will be used to formally transfer a participant from one CUTIE clinic to another.

7.9.5 Participant/Parent Dropout

A participant is a dropout if the participant is living, but the child and family are not completing follow-up contacts. Examples of a dropout include a participant whose parent refuses telephone contacts as well as clinic visits, a participant who has moved and cannot be located, or a participant or parent/guardian with a long-term illness preventing their participation in a clinic visit or telephone interview and who has no proxy available.

When this occurs, and to the extent possible, Coordinators should determine the willingness of the parent/guardian to work on solutions to overcome barriers to participation. If the parent/guardian is absolutely unwilling to return to clinic visits, negotiate continued participation in telephone follow-up assessment and data collection on inter-current illnesses and medical are visits. To the fullest degree possible, Coordinators should document possible events and medical care visits per protocol instructions. If the parent/guardian cannot be converted to continue telephone contact at a minimum, record participant reasons for withdrawal and date of withdrawal on an Informed Consent Tracking Form (ICT).

7.9.6 Participant is Lost to Follow-up

If all efforts to locate a participant and his/her family have failed, then the participant is considered Lost to Follow-up. Record on the RCF whether participant's vital status is known or unknown and last date of known contact with CUTIE. To the fullest degree possible, Coordinators should document all possible events and medical care visits per protocol

instructions. Because parents have already signed a consent form and a medical release form medical care records should be obtainable as long as the consent has not been rescinded.

7.9.7 Change in Parent/Guardian During Study Follow-Up

If there has been a change in a participants parent/guardian during the follow-up, or a parent/guardian is unable to communicate clearly during the interview, another family member or proxy may be used during study follow-up provided they can provide accurate data and are willing to assist the parent/guardian (see section 7.7).

7.9.8 Consent is Revoked or Altered

Participation in CUTIE is voluntary. At any time a parent/guardian can decide to change their mind and refuse continued consent. In this event, Coordinators and Investigators should attempt to discuss the reasons behind the parent decision, and try and negotiate levels of participation that can continue. However, if consent is refused, there can be no continued data collection.

7.9.9 Recurrent Event

If participant or parent/guardian is temporarily hospitalized, or otherwise unable to continue follow-up visits because of a recurrent event or other health condition, discuss importance of returning to follow-up after recovery. Conduct weekly follow-up phone calls to determine status of participant.

7.10 Attempted Recovery of Dropouts

When applied systematically, dropout recovery methods have been demonstrated in clinical trials to re-engage participants who have become inactive. While not originally conceptualized in this manner, this approach incorporates the use of good reflective-listening and directive skills that can elicit barriers to participation from subjects and their family. This information is then used to problem-solve with the parents/guardians about methods to overcome the identified participation barriers. Finally, an essential component of dropout recovery is the application of motivational interviewing methods in an attempt to further elicit and clarify the participant or parent/guardian's reasons for discontinued participation.

The approach to dropout recovery will involve the following steps:

1) contact the participant's parent/guardian
2) identify and discuss reasons for withdrawal
3) negotiate solutions to overcome barriers
4) apply motivational interview methods

If the Coordinator is not successful in re-engaging the parent/guardian, then the principal investigator should initiate contact. Contact by a new member of the staff results in new perspectives and is encouraged in dropout recovery.

7.10.1 Contact the Participant's Parent/Guardian

Attempt to contact the participant's parent/guardian. When a follow-up clinic visit or phone contact has been missed without advance warning, the Study Coordinator should first attempt to make contact directly by phone. If the Coordinator finds the telephone number is no longer correct or operational, then an attempt should be made to contact the proxy for the participant. Proxy contact information will have been previously supplied and updated by the parent/guardian and is documented on the Participant Contact Form (PCF). The proxy may be asked to have the family contact the study staff or to find out whether the participant is still in the area and his/her status. The Study Coordinator may also send a letter by certified mail, asking the family to contact the study staff. Record the results of all attempts to contact the participant either by phone or by mail on the participant's Record of Contact Log (RCF).

Attempt to contact the participant's physician, by letter or by phone, for the participant's current address and/or vital status. Record the result of the attempt to contact the participant's personal physician on the RCF. Other staff in the physician's office, such as the nurse, may also be asked to provide this information.

Other sources to investigate the participant's whereabouts include parent/guardians' employers, internet directories, Social Service agencies, the Department of Motor Vehicles, the Police Department, etc. In each instance record the results of the inquiry on the RCF.

7.10.2 Identify and Discuss Reasons for Missed Contacts

Continued follow-up data collection on all participants is critical for successful completion of the study. Identifying the reasons behind the missed contacts may result in required data documentation (i.e. adverse event reporting), and will also provide the Coordinator with information to work out solutions that can be negotiated with the parent/guardian to continue the follow-up data collection.

In some cases, discussing the reasons for withdrawal will reveal that the barriers to participation are solvable. It is important to use good reflective-listening and directive skills to elicit barriers to participation from participant. When engaging in reflective-listening, your tone is empathetic, accepting and open.

Here are some general guidelines for reflective-listening:

- Do more listening than talking
- Respond to what is personal rather than to what is impersonal, distant, or abstract.
- Restate and clarify what the other has said, without asking questions or communicating what you, the listener, feels, believes, or wants.
- Try to understand the feelings contained in what the other is saying, not just the facts or ideas.

- Work to develop the best possible sense of the other's frame of reference while avoiding the temptation to respond from your frame of reference.
- Responding with acceptance and empathy, not with indifference, cold objectivity, or fake concern.

7.10.3 Negotiate Solutions to Overcome Barriers

When major barriers to participation involve logistical obstacles, first try to identify alternative strategies that the participant's family may use to overcome these obstacles. If these alternative strategies fall short or are not available, then offer reasonable logistical assistance provided by study resources. For example, we already mentioned that if a patient's parent/guardian absolutely refuses to come back to clinic, Coordinators can offer to continue follow-up over the phone.

7.10.4 Apply Motivational Interview Techniques

Motivational interviewing can help patients identify and change behaviors that may be preventing them from optimal management of a particular condition. Coordinators can use motivational interviewing techniques to encourage participant's parent/guardian's to reconsider their decision to withdraw, and explore possible compromises. As with reflective-listening, your tone should be empathetic and non-judgmental. However, with this approach you actively help the participant steer themselves toward a compromise or common goal.

Here are some general guidelines for Motivational Interviewing:

- Express empathy – convey an informed understanding of the other person's predicament
- Avoid argument – arguments only cause the other person to become defensive
- Support self-efficacy – encouraging and reinforcing the other person to say self-affirming statements can help the him/her believe in his/her ability to make a change
- Roll with resistance – instead of falling into the argument trap, find ways redirect and build on the other person's negative statements. Questioning, asking for clarification, elaborating on a point, or humor are all good ways to roll with statements of resistance.

7.11 Locating Difficult-to-Follow Participants

If the initial call to the number provided by the participant at last contact is unsuccessful, the first telephone tracing step is to contact Directory Assistance in an attempt to verify the address provided and to obtain a new telephone listing. If the address is verified and the phone number is unlisted, send a letter to the participant requesting that the participant telephone the Study Coordinator. If attempts to obtain a listing or verify the address are unsuccessful, secondary sources will be used. Identifying the order of tracing sources for all cases is difficult, though the typical tracing will follow the procedures described below.

The first step is to obtain from the participant's record the contact person (proxy) listed by the participant at enrollment and during follow-up contacts. A Proxy is contacted to determine if they can provide the current address or telephone number of the participant. If successful, the Study Coordinator enters the updated location information on the PCF and attempts to contact the participant.

If this is not successful, depending on the participant's last residence, a decision is made whether to consult the city directory information or to contact the local post office. If the address is rural, the postmaster is called, since, in rural areas, the postal carrier or postmaster typically knows individuals in their service area. Since address corrections should have been obtained from the mailing of the advance letter, calls are not made to urban post offices.

Chapter 8: Compliance

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Chapter 8: Compliance

8.1 Overview Adherence Compliance

Ensuring adherence to the CUTIE study protocol may be a challenge for the clinic staff, requiring as much or more effort than that put into recruitment. Enrollment is only the beginning. Once patients are enrolled in the study, participant compliance to study protocol is crucial to the study's success.

Adherence to study protocol and follow-up procedures will be examined through data reports and monitoring visits.

8.2 Follow-up Visits and Telephone Contacts

Reports describing adherence to the study contact schedule clinic-specific and overall, will be distributed to the Principal Investigators (PIs) and Project Coordinators.

Steps will be taken within the research study to assist a clinic with lagging performance. Reasons for missed visits and telephone calls should be noted on the Record of Contacts Form (REC) at each site. This information will be important in assessing adherence to protocol during clinic monitoring visits.

Each contact is to be scheduled within 10 days of the target date for that contact, and all attempts should be made to complete a contact within the protocol specified 20-day window. However, to avoid missing data altogether, a contact can be conducted outside of this window, provided that it does not fall too close to next regularly scheduled contact. For a detailed discussion of visit scheduling, refer to MOP Chapter 7: Follow-up Contacts.

~~8.3 Medication Compliance~~

The CUTIE Study does not have a medication associated with the study.

8.4 Setting the Scene for Good Adherence

Setting the stage for good adherence can be facilitated in a number of ways:

- Discussion of the Informed consent
- Clinic atmosphere and staff attitude
- Discussing perceptions of personal benefit
- Having the endorsement of others

8.4.1 Discussion of the Informed Consent

Much of the potential for poor adherence can be negated from the start by excellent explanations of the role of the participants and their families in meeting the goals of the study. The explanation should be simple enough to be understood and remembered, and not so detailed that it is overwhelming and alienating.
The participant handbook outlining the phases of the study and the procedures involved

with other important information such as phone numbers, contact persons and even transportation and parking information will be very helpful. All written and printed materials, however, should be an adjunct to friendly face-to-face communication, where the parents/guardian and participant are encouraged to ask questions.

If the parent/guardian does not ask questions and seems to be too willing to enroll without adequate thought, the Coordinator/Investigator should review a list of basic information. Such a list would cover the length of commitment to the study, and the requirement to have the study images performed and blood drawn.

When parents/guardians give consent for their child to participate in a research study, those that are truly informed will be the best compliers.

8.4.2 Clinic Atmosphere and Staff Attitude

The clinic should be a pleasant place for the participants and their family to come to. The staff should have a warm, welcoming and supportive attitude. Even if the physical setting is a standard out-patient clinic, the participants and their families should have a very positive experience when they come for their CUTIE study visits. Never forget that they are volunteers. Waiting should be minimal and staff should greet each participant in a personal manner and develop a relationship with each one. At each visit the participant and their family should be told sincerely how much the staff values their participation and how important they are to this research effort.

8.4.3 Discussing Perceptions of Personal Benefit

Most study participants enter a study because they perceive some personal benefits to be gained. These should be emphasized; they include:

- Close medical surveillance
- Standard testing providing information about UTIs
- Status of being an important part of a study to advance medical knowledge

8.4.4 Having the Endorsement of Others

Consensual validation of the study by other health care professionals may be a key feature both in recruitment and in adherence. Research study literature has more than one example of studies that have been virtually derailed due to opposition voiced in the media or by health care providers. It is always good policy to inform your medical colleagues in the target community of the rationale and goals of the study, and ask them to endorse it.

8.5 Maintaining Good Adherence

There are also many approaches to maintaining good adherence, including:

- Providing Regular feedback
- Memory "joggers"
- Convenience
- Attention to Concomitant illness or treatments

8.5.1 Providing Regular Feedback

Feedback is an effective reinforcer. Parents/guardians and participants should be given regular feedback on their progress of the study. Emphasize the important role each person is playing in the success of the study and praise them for their commitment. Other things to consider are a study newsletter, birthday cards or other holiday cards maintaining contact even outside regular protocol contacts.

8.5.2 Memory

In order to adhere, parents/guardians have to remember what to do. Most of them will appreciate memory "joggers" whether they have poor memories or simply very busy lives. Some suggested techniques are:

- give all instructions in writing as well as verbally.
- use reminder postcards or telephone calls prior to clinic visits
- use appointment cards with important information on the reverse (for example, contact person and phone numbers in case of adverse events, reminders of procedures)

8.5.3 Convenience

The ease of traveling to the clinic can affect visit adherence. Illness, disability, bad weather, parking difficulties, expense or inconvenience of public transportation, home/social problems can all cause cancellations and no-shows. A cancellation or noshow should flag a participant as someone who needs extra support to adhere to the visit schedule.

The families should not feel judged or censured for missing a visit. Staff should contact the parent/guardian immediately and be very supportive in finding a way to complete the visit. There should be a simple assumption that the visit will be made-up, and practical assistance provided to ensure adherence.

8.5.4 Attention to Side Effects Adverse Events

The CUTIE Study does not have a study medication and will therefore not have side effects of study medication. However, adverse events not related to the study still need to be recorded.

8.5.5 Attention to Concomitant Illness or Treatments

In a study of this length, many participants will have an illness at some time, even if only a cold, which will cause the child to be treated. Staff should emphasize the importance of reporting all illnesses to the clinic staff.

8.6 Undue Pressure to Comply

Although staff is expected to initiate measures to prevent and combat poor adherence, they must be sensitive to the potential for crossing the line and exerting undue pressure on the participants and their family. Participants are volunteers who are free to quit at any time and their adherence must be voluntary, not forced. At each clinic there will be a few "difficult" participants who will test your skills, patience and good humor; the challenge is to have them remain in the study because they want to, not because they were persuaded against their will to remain.

Any individual staff person who is having problems with a parent/guardian and child or who feels that a personality conflict has developed, should initiate discussion among the center's study staff to receive input on developing a resolution. Recognizing when, in spite of your best efforts, you do not have the answer to the problem is a sign of experience and professionalism.

Chapter 9: Participant Safety and Adverse Events

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Chapter 9: Participant Safety and Adverse Events

9.1 Participant Safety

Participant safety always takes priority over all else. The International Conference on Harmonization's general principles of Good Clinical Practice will be followed. These principles dictate, first and foremost, that we have weighed and will continue throughout the study to weigh the anticipated benefits versus the foreseeable risks to all participants. Participants will be fully informed of these risks before they are enrolled. The study's leadership will continually review the medical literature to determine any new findings that might substantially affect the study's rationale or justification, and for new or previously unforeseen risks that must be conveyed to participants.

Responsibility for monitoring patient safety during the study is shared by each clinical center's IRB and the site PI. In order to ensure appropriate monitoring can occur, clinics are responsible for following informed consent procedures, taking measures to ensure participant confidentiality, adhering to HIPAA regulations, and closely monitoring and reporting adverse events. Timely reporting of all untoward events occurring during the study is the only way to ensure that these groups can conduct appropriate monitoring of patient and study safety. Study procedures for monitoring and reporting of events are detailed below. Study monitoring of compliance to these procedures is described in the Quality Assurance and Quality Control Chapter 12 of the CUTIE MOP.

9.2 Monitoring Events at the Clinical Sites

Data collection of adverse events allows appropriate safety monitoring of subjects. In CUTIE, in addition to safety monitoring, data collection on adverse events is necessary for endpoint ascertainment. For both of these reasons, complete, accurate, and timely information is crucial. Detecting and reporting serious adverse events is the responsibility of the Principal Investigator, although the actual data collection and reporting is often delegated to the sites Project Coordinator.

During the informed consent process, the parent or guardian will have been asked to report all fevers and illnesses to the clinic. Appropriate contact information will be provided. A patient handbook containing a record diary will be provided to allow simple recording of fevers, illnesses, and new concomitant medications, to insure good recall at follow-up contacts.

At each follow-up telephone and clinic visits, parents will be asked to report on all untoward medical occurrences since the last study contact. Data collection on adverse events monitoring is triggered by the question "Has your child had any health problems since the last study contact?", on the Protocol Scheduled Follow-Up Questionnaire. Additional questions querying about any medical care visits, or newly prescribed medications all provide mechanisms for monitoring of adverse events.

The study will collect information on all reported adverse events, medical care visits, and hospitalizations and deaths.

9.3 Definitions related to Adverse Experiences

9.3.1 Adverse Events

An adverse experience or adverse event (AE) is any untoward medical occurrence in a patient.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient or subject and/or observed by the physician or medical staff.
- Laboratory abnormalities of clinical significance.

Disease signs, symptoms and/or laboratory abnormalities already existing prior to enrollment are not considered adverse experiences unless they re-occur after the patient has recovered from the pre-existing condition, or represent an exacerbation in intensity or frequency.

9.3.2 Serious Adverse Events

A serious adverse experience or adverse event (SAE) is any adverse event that results in any of the following outcomes:

- Death
- A life-threatening experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The distinction between an adverse event and a serious adverse event is based on the definition for serious adverse events, and not on the severity of an event, i.e. serious vomiting is not considered a serious adverse event except if it requires hospitalization.

9.3.3 What Adverse Events are CUTIE Reportable Events

1) All serious adverse events are reportable.
2) Non-serious adverse events that are:
   - Other events/experiences that were not expected in a patient on prophylaxis antibiotics

Some sites IRB's may require IRB reporting of other advents or experiences that do not fit the description above. This additional reporting would be the sites responsibility (as are all IRB reporting), and not part of study data collection.

9.4 Adverse Event Data Collection

The CUTIE Study requires all clinical sites to report adverse events using the Adverse Events Data Collection Form (AEF).

9.4.1 The Adverse Events Data Collection Form (AEF)

All CUTIE adverse events are recorded onto the AEF form. One AEF is completed for each individual diagnosis or complaint. The AEF form is designed to collect both non-serious and serious adverse events data. In addition to documenting all reported adverse events, the AEF form includes a very short interview administered to the parent/guardian regarding the illness.

The AEF form is triggered by responses to questions on the Protocol Scheduled Follow-up Form (FUP), as well as questions on the Medical Care Notification Form (MCN). Conversely, the AEF form has a question that could trigger the need to collect an MCN form.

Not every AEF will have an associated MCN form, if no medical care was sought for the event. Nor will every MCN form have an associated AEF, as some medical care visits may be associated with a well-child routine physical exam, or other reasons that are not adverse experiences.

9.4.1.1 MCID Number on the AEF

When there is an association between an AEF and MCN form, the linkage between adverse events and endpoint forms is critical to study data management. This link is done through the Medical Care ID Number, or MCID#. The MCID is assigned and associated with each medical care visit, not necessarily each adverse event. This is an important distinction to understand. Each adverse event corresponding with a medical care visit (this is the first medical care visit associated with the event), must have the MCID number associated with that first medical are visit recorded on the AEF in the space provided. The process of assigning MCID #'s is described in detail in Chapter 10: Medical Care Abstraction and Endpoints.

It is possible that there are multiple AEFs associated with one MCN, in this event, the MCID # from the associated MCN should be recorded on all AEFs that report on events/symptoms occurring as part of the medical care visit. There will not be multiple MCNs associated with any one AEF since the link is only to the first medical care visit related to an event.

9.4.1.2 Adverse Event Coding

Coding of adverse events is done at the time of data entry on the AEF. During data entry of the AEF form, question X is the parent reported event or symptoms. The following field in the DMS includes a feature that provides a search and lookup table of COSTART coding terms. This feature has been added to make the process very user friendly for the sites. Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), is a terminology developed and used by the Food and Drug Administration (FDA) for the coding, filing and retrieving post marketing adverse reaction reports. COSTART contains unique code-able events that provide a variation in vocabulary commonly used by those who submit adverse event reports. A listing of all COSTART code-able terms is provided at the end of this Chapter.

9.5 Reporting Processes for Adverse Events

9.5.1 Adverse Event Reporting to the DCC Not applicable to CUTIE

All adverse event reporting needs of the clinical sites are completed by the prompt data entry of the AEF form into the study DMS. All AEF forms should have data entry completed within 5 working days upon hearing of an event.

9.5.3 Reporting to Site IRBs

Each clinical site is responsible for any IRB or regulatory reporting of adverse events as required by their institution.

9.5.4 Reporting to Data and Safety Monitoring Board

Since CUTIE is an observational study, an independent Data and Safety Monitoring Board was not established. The site PIs are charged with approving and/or making recommendations to the protocol, as well as monitoring recruitment and retention and reviewing data for safety.

Chapter 10: Medical Care Abstraction and Endpoints

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Chapter 10: Medical Care Abstraction and Endpoints

10.1 Overview

The proportion of children who have any renal scars assessed on the outcome DMSA scan will serve as the principal analysis variable. Secondary endpoints include the proportion of children with severe scarring, the proportion of children who have at least one recurrent UTI, and the proportion of children who become "treatment failure".

Suspected recurrent UTI events will be reviewed and adjudicated to determine if they meet the RIVUR criteria for a secondary endpoint. The definition of recurrent $_{F/S}$UTI requires the presence of (1) fever or urinary tract symptoms1, and (2) pyuria based on urinalysis, and (3) culture-proven infection with a single organism. A UTI will be defined as recurrent only if its onset occurs more than 2 weeks from the last day of treatment for the preceding UTI, or following a negative urine culture.

This Chapter will focus primarily on data collection and procedures related to data collection and subsequent assessments of recurrent UTIs. Chapter 3: Radiology provides data collection and adjudication procedures related to radiographic images at baseline, 12 months, and end of study. The occurrence of recurrent UTIs in CUTIE participants may require the scheduling and collecting of additional DMSA scans during the study. The process of determining the need for additional DMSAs is covered at the end of this chapter.

10.2 ~~10.2~~ Definition of ~~UTI~~ Renal Scarring Primary Endpoint

The incidence and extent of renal scarring will be determined 24 months after the index UTI episodes using renal scintigraphy (^{99}Tc dimercaptosuccinic acid (DMSA) scan). Children who experience "treatment failure" as defined in the RIVUR Study will have the outcome scan approximately 4 months later.

Renal scarring will be defined as decreased uptake of tracer associated with loss of contours or cortical thinning. In order to quantify the extent of renal scarring, each kidney will be divided into 12 segments and a five level grading system will be applied. Severe scarring will be defined as the presence of grades 3 or 4 scarring on at least one kidney.

10.2.1 Definition of Recurrent UTIs Secondary Endpoint

The definition of recurrent $_{F/S}$UTI (the CUTIE ~~primary~~ secondary study endpoint) requires the presence of:

1. Fever or urinary tract symptoms, and …
2. Pyuria based on urinalysis, and …

1 Must occur within ± 24 hours of initiating work-up for UTI.

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3. A culture-proven infection with a single organism

A UTI will be defined as recurrent only if its onset occurs more than 2 weeks from the last day of appropriate treatment for the preceding UTI or following a negative urine culture, or it is an infection with a new organism.

Suspected recurrent UTI events will be reviewed and adjudicated by the UTI Classification Committee (UCC), established for RIVUR, to determine if they meet the CUTIE criteria for a primary endpoint.

It is important to note that if a potential endpoint is determined not to meet the pre-specified criteria for an $_{F/S}$UTI event, it does not mean that the event did not occur. Rather, it means the event did not meet the CUTIE criteria for a study endpoint.

10.3 Data Collection Forms required for assessing a UTI Endpoint

The following data collection forms are required to document a potential UTI endpoint:

Medical Care Notification form (MCN)
Medical Care Abstraction Form (MCA)
Urine Specimen Results Form (USR)

In addition to providing the data and information about potential UTI events on the required data collection forms (MCN, MCA, USR), sites may need to provide additional essential source documents needed in the endpoints review process.

10.4 Clinical Site Procedures for Data Collection

Each site contributes to the endpoint classification process by promptly identifying and reporting any potential study endpoints. The process begins with the data collection at the clinical sites.

10.4.1 Identification of Potential UTIs

In order to assure that the study captures every potential endpoint. Data are expected on all participant medical care visits where the child had urine collected for analysis OR received medical care for symptoms that include fever, rash, abdominal or flank pain, diarrhea or loose stools, urinary urgency, painful urination, foul-smelling urine, or for children less than 4 months old, failure to thrive, dehydration, or hypothermia. A medical visit includes any doctor visit, clinic visit, ER visit, or hospital admission. This includes ~~well-child visits,~~ s sick visits made to a CUTIE clinic at a non-protocol scheduled follow-up visit, as well as a protocol scheduled follow-up clinic visit when the Investigator suspects there are symptoms to indicate the participant is sick.

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Parents/guardians will be asked to document all medical care visits the participant makes in the participant handbook/diary. They will also be asked to call and report any illnesses. These calls (if received) will be recorded onto the Participant Records of Contact Log

(RCL) and will trigger the documentation process prior to recording on data collection forms.

Coordinators must collect sick visit data from wherever the participant sought care. Some sick visits may occur at the CUTIE clinics, so sick visit data will be readily available. Other sick visits will occur at non-study clinics, ERs, or hospitals. In these cases, Coordinators will have to collect data on the reported visits from the participant's primary care physician or other provider. For most participants, a combination of both will be required to capture all non-study medical care throughout the trial.

In addition to calls from parents/guardians reporting illnesses, the Protocol Scheduled Follow-up Form (FUP) includes questions that trigger the need for endpoints data collection including ~~'How is your child feeling today?',~~ 'Has your child visited a doctor?'~~,~~ ~~etc...~~ Other data collection, such as a change in concomitant medication use also provides a flag to the coordinator that a medical care visit occurred. A review of the participant handbook/diary will also allow recall of previous care visits since the last contact.

All medical care visits, including a doctor visit for an expected well child visit or physical exam where urine was collected or symptoms related to UTI were documented, will require some data collection on an MCN and MCA form in order for the UTI Classification Committee to determine whether or not a study endpoint has occurred.

10.4.2 Medical Care Notification Form (MCN)

The MCN form is based on an interview with the parents, and begins the official process of data collection for UTI endpoints. This form is used to document all medical care visits, including protocol scheduled follow-up visits where the child is noted to be ill or the clinic provides non-study sick child care (beyond standard follow-up data collection). One form should be collected for **every** medical visit where the child had urine collected for analysis **OR** received medical care for symptoms that include fever, rash, abdominal or flank pain, diarrhea or loose stools, urinary urgency, painful urination, foul-smelling urine, or for children less than 4 months old, failure to thrive, dehydration, or hypothermia.. A separate MCN form is completed for each subsequent visit (follow-up visit) on the same event. If a participant is hospitalized, and during the hospitalization is transferred to a second hospital, the second hospitalization should be treated as a separate medical visit. There are questions on the MCN that allow coordinators to fully describe the situation and link the two hospitalizations together.

The MCN serves two main functions:

1. It captures the information the coordinator needs to request medical records.
2. It alerts the DCC of potential endpoints.

The MCN form may trigger adverse event data collection as well. As such, timely entry of this form is extremely important. Coordinators should complete an MCN as soon as possible after being notified that a medical visit occurred.

The MCN also includes a short parent/guardian interview on the child's history of -fever and possible UTI symptoms, as well as resource allocation data on events. Since the parent/guardian's ability to recall events is important to this data collection, it is important to begin the data collection process as soon as the Coordinator is aware that a medical care visit occurred. The participant handbook/diary, will also help with parent recall of events.

As soon as you have enough information about where/when the medical care visit occurred, immediately begin the process of requesting medical records and completing the MCA form. This can often be a timely process and is critical for participant safety monitoring.

Refer to the MCN QxQ for item specific instructions.

10.4.3 Assignment of Medical Care ID Numbers (MCID)

Medical Care ID numbers (MCID NUMBER) are the way in which multiple data collection forms are linked to non-protocol medical visits. The MCID number format consists of 5 numbers, followed by a two-character site code. Coordinators will receive pre-printed MCID Labels which they will use as needed. MCID numbers should be used/assigned sequentially starting from the lowest number. MCID number labels should be affixed to all source documentation of medical visits (copies of external medical records, urinalysis reports, etc.)

An MCID NUMBER is assigned by the coordinator at the time that the MCN is completed. For every MCID NUMBER there will be an associated MCN form. This same MCID number will be used/entered to link together all forms associated with a medical visit, including the Medical Care Abstraction Form (MCA), and potentially the Urine Specimen Results Form (USR), Adverse Event Forms (AEF), and/or DMSA radiology forms.

Every clinic or doctor visit requires an associated MCN form, and therefore a unique MCID NUMBER. This means that even follow-up visits to previously reported events will require new MCN forms and new MCID numbers. There are questions on both the MCN and MCA forms that allow coordinators to reference the MCID numbers of related previous medical visits. For example on the MCA form coordinators must answer the following:

3. Is this a follow-up visit to a previously reported medical visit?.....Y N → Go to Item 6

4. Date of previously reported medical visit? ..... ☐☐/☐☐/☐☐☐☐

5. MCID Number associated with the previously reported visit:..... ☐☐☐☐☐☐☐

MCID numbers and labels will be provided to the clinics by the DCC. If more MCID numbers and labels are needed, coordinators should contact ~~the DCC at 1-866-257-7242~~Sheila Burgard at (919) 966-4072.

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10.4.3.1 Clinic Tracking of MCID Numbers

The DMS system is equipped with a number of reports that will help coordinators track and correctly assign MCID NUMBERs.

The 'MCID Number Inventory' is provided as a tool for sites to track which MCID NUMBERs have been assigned. This report will present a listing of all MCID NUMBER currently listed on MCN forms in the DMS, sorted by MCID NUMBER. This is an easy way for coordinators to see which MCID NUMBER was assigned last, and will help him or her determine which MCID should be assigned next. An example of the report is presented in Table 10.1 below.

Table 10.1 MCID Number Inventory (by MCID)

MCID	Participant ID	Form Version	Contact Occasion	Sequence Number
00024KH~~BF~~	~~BF00389~~KH00389	MCNA	02	02
10016KH~~BF~~	KH~~BF~~12345	MCNB	03	01
10057KH~~BF~~	KH~~BF~~00389	MCNB	02	03

Another report is the 'MCID Form Inventory'. For this report, the coordinator is prompted to enter an MCID NUMBER, then the DMS generates a list of all forms associated with that MCID. And example of this report is presented in table 10.2 below.

Table 10.2 MCID Form Inventory

Form Inventory for MCID: 00024BF

Participant ID	Form Code	Contact Occasion	Sequence Number
BF00389	MCNA	02	02
BF00389	MCAA	02	02
BF00389	USRB	02	02
BF00389	AEFA	02	02

A third report called the 'Participant MCID Report' prompts the coordinator to enter a participant ID. The DMS then generates a list of all MCID numbers used for a particular participant, as well as all other forms linked to each MCID. See- table 10.3 below for an example.

Table 10.3 Participant MCID Report

Participant ID	MCID	Form Code	Contact Occasion	Sequence Number
BF00389	00024BF	MCN	02	01
		MCA	02	01
		USR	02	01
	00032BF	MCN	02	02
		MCA	02	02
		USR	02	02
		AEF	02	02

A final report available in the DMS is the 'MCID Tracking Report.' This is a more comprehensive version of the MCID Number Inventory. It lists all MCIDs used in the DMS, along with all participant IDs and all forms associated with each MCID, sorted by MCID.

Table 10.4 MCID Tracking Report (Listing of all MCID's and Associated Forms)

MCID	Participant ID	Form Code	Contact Occasion	Sequence Number
00012BF	BF00125	MCN	02	01
		MCA	02	01
00024BF	BF00389	MCN	02	01
		MCA	02	01
		USR	02	01
00032BF	BF00389	MCN	02	02
		MCA	02	02
		USR	02	02
		AEF	02	02

10.4.4 Contact Occasion and Sequence Numbers for Source Documentation

Procedures for assigning contact occasions and sequence numbers are covered in Chapter 13: Administrative Procedures. The challenges of these assignments ~~is~~ are felt most often during endpoint and adverse event data collection, which most commonly occurs between contact occasions.

It is important to note that the forms associated with a medical visit may not all have the same seq#. For example, let's say that participant BF00389 had two medical visits between the 02 and 03 contact occasions. The first medical visit (MCID 00024BF) was a visit for a broken arm and no urine was collected. The second medical visit (MCID 00032BF) was a

sick visit for a suspected UTI, so urine was collected. Although the urine collection occurred at the second medical visit where the MCN contact occasion and seq# are both 02, the USR form should be labeled with contact occasion 02 and **seq# 01**, because it is the first time since the last study contact that a USR form was completed. See table 10.5 below:

Table 10.5

Participant ID	MCID	Form Code	Contact Occasion	Sequence Number
BF00389	00024BF	MCN	02	01
		MCA	02	01
	00032BF	MCN	02	02
		MCA	02	02
		USR	**02**	**01**

Although the seq#s differ for the forms associated with the second medical visit, they are linked by the MCID NUMBER 00032BF, which is specified on each form.

10.4.5 Medical Care Abstraction Form (MCA)

For each medical care visit reported on an MCN form, an associated Medical Care Abstraction Form (MCA) is required. The MCA form has been designed to collect medical care visit data from primary care physicians, clinics, ER's and hospital admissions. Even if the coordinator cannot obtain access to outside medical records, he or she must complete an MCA form and indicate on the MCA that access to medical records was not granted.

10.4.6 Notification of Potential Endpoints to the DCC

The DCC is notified of potential study endpoints through the completion of the Medical Care Notification form. The DCC monitors daily the completion of MCN forms and tracks the completion of data forms linked to each MCN.

10.4.7 Additional Source Documentation

In addition to the CUTIE case report forms, supporting source documentation may be requested from the clinical site. The UTI Classification Committee (UCC) (?) relies mainly on DMS data in order to determine whether endpoint criteria were met for a particular event. However, the committee does reserve the right to request additional source documentation if needed.

All source documentation requested and submitted to the DCC must include the MCID number, participant ID number, contact occasion and sequence number corresponding to the associated MCN and MCA entered into the DMS. Source documentation must be filed locally in the participant's study binder/file.

An Endpoint Source Documentation Cover Sheet, (ESD) should accompany all source documentation being sent to the DCC. Use a separate cover sheet for each MCID number.

All source documentation sent to the DCC must have personal identifiers masked. Participant name, social security number, physician and other individual names, medical record numbers, and other identifiers deemed confidential by local regulations must be masked or adequately blacked out prior to submission to the DCC.

Masked and labeled supporting documentation and cover sheet can be faxed to:

CUTIE DCC
919-962-3265

_____or mailed to:

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CUTIE DCC
CSCC-UNC Biostatistics Dept.
137 E. Franklin Street, Suite 203, CB# 8030
Chapel Hill, NC 27514-4145

10.5 UTI Classification Committee (UCC)

10.5.1 Introduction

Given the range of CUTIE clinical sites, there will be differences in how participants are treated and how certain diagnoses are made. The CUTIE UTI endpoint has a very specific definition, and all criteria must be met in order to classify a UTI as a CUTIE endpoint.

In order to eliminate any site-to-site differences and remove all possibilities of endpoints being determined subjectively, all reported medical care visits (clinic, primary physician, hospitalization, etc…) will require data collection. Those visits where a potential UTI is identified will be reviewed and classified by UCC, who will use standardized criteria to adjudicate each event according to the study definitions. At the end of the trial, when reports are generated on the study data and a comparison is made between the number of events in one treatment group versus the other treatment group, investigators can be confident the events reviewed by the UCC all met the same criteria and were supported by source documentation.

10.5.2 Role and Responsibilities (Who determines CUTIE endpoints?)

The Clinical Endpoints Committee at UNC serves as an independent committee responsible for defining, reviewing and classifying CUTIE endpoints. Every potential study endpoint will eventually be sent to the UCC. The UCC will then review each event through data review by computer algorithm or UCC adjudication, and determine whether each meets the pre-specified endpoint criteria.

10.5.3 Review and Adjudication of UTIs

The DCC monitors entry of the MCN forms for every medical visit. When an MCN form entered into the DMS indicates a potential study endpoint, the DCC compiles the data from all DMS forms referencing that MCID# for that visit. This compiled data is sent to two randomly selected members of the UCC. Each of the two UCC members is considered a reviewer for that event. Based on the compiled data report received from the DCC, each reviewer must classify the event and complete the UTI Endpoint Classification and Adjudication Form (ADJ) in the DMS.

Once the two reviewers from the UCC have classified a UTI through entry of the ADJ into the Data Management System, the DMS will compare the two records. The DCC will monitor all UCC data entry daily. If adjudication is necessary for a medical visit, the DCC will alert the UCC, and the UCC will meet or set up a call as soon as possible to come to a final decision on items that need adjudication.

Timeliness of the review, classification, and adjudication processes is essential to prompt determination of study endpoints and potential treatment failures.

10.6 Clinical Procedures for UTIs

It is important to remember that all suspected UTIs should be treated according to standard clinical care, regardless of whether study endpoint criteria are met. If a potential UTI is determined not to meet the pre-specified criteria for an $_{F/S}$UTI or $_{F}$UTI, and is determined not to be a study endpoint, it does not mean that the UTI event did not occur. It only means that the event did not meet the CUTIE criteria for a study endpoint. This is where clinical care vs. study procedures may appear to conflict.

In addition, the occurrence of a UTI or an endpoint does not mean that study medication is discontinued. Discontinuation of study medication is only mandated for participants defined as treatment failures (Section 10.7). Investigators are responsible for participant safety and decisions based on clinical care as needed.

10.7 Treatment Failure

The designation of treatment failure is based on frequency and rate of $_{F/S}$UTI recurrence, or identification of new or worsening renal scarring found in subsequent follow-up DMSAs.

10.7.1 Definitions of Treatment Failure

Although treatment will not be provided as part of this observational study protocol, we will characterize the children in the CUTIE Study in terms of the criteria used to define treatment failure in the RIVUR study.

In any participant, the occurrence of two $_{F}$UTIs **or** a total of four $_{F/S}$UTIs during the study

period **or** an interim 12-month scan showing new scarring at a site different from the index APN or worsening scarring evidenced by extension of a preexistent scar seen on the baseline DMSA scan will be classified as a treatment failure. In treatment failure cases where new or worsening scarring is observed on the 12-month DMSA scan, the interim scan may serve as the outcome DMSA scan.

Children whose baseline DMSA scan shows grade 3 or higher scarring in either kidney will have a repeat DMSA performed at the time of any recurrent $_F$UTI. If additional renal segment involvement is observed in comparison with the baseline scan,, these children will also be categorized as treatment failure and have an outcome DMSA scan at approximately 4 months following the $_F$UTI. If no further damage is apparent, they will continue in the study as assigned.

10.7.2 Identification of Treatment Failure

The recurrence of a CUTIE study UTI is determined by either matching UCC classification records or the UCC adjudication process, and is based on data collected at the sites. The classification of UTIs must be very timely, as a determination of CUTIE UTI may result in a determination of treatment failure or the need for DMSA scheduling (for participant safety). Prompt completion of data entry forms and submission of source documentation to the DCC (if requested) will assure that such determinations can be made in timely manner.

10.7.3 Notification of Treatment Failures from DCC to the Sites

UTIs determined by the UCC to be study endpoints will only be reported back to the clinical sites if the UTI now classifies the participant as a treatment failure, necessitating the discontinuation of study medication and/or scheduling of additional radiographic scans.

Once a UTI has been classified and it is determined that treatment failure criteria have been met, the DCC will send within 24 hours a memo via email to the site Principal Investigator (PI) notifying the PI that the participant has met treatment failure criteria, instructing the PI to discontinue study medication and refer the participant to standard care, and giving further instruction as necessary. The DCC will also mail a paper copy of the memo to the PI. PIs will be asked to notify the DCC when the memo is received.

10.7.4 Study Procedures for Treatment Failure Participants

All children categorized as treatment failure (Section 10.7.1) will be offered or referred to usual clinical care, undergo a DMSA scan 4 months post failure unless the interim 12-month scan is appropriate for use as the outcome scan, and continue follow-up until the 24-month exit.

10.7.4.1. Procedures for Participants with ≥Grade 3 Scarring on Baseline DMSA

For participants whose baseline DMSA scan shows grade 3 or higher scarring in either kidney, the study procedures for treatment failure are triggered at the first recurrence of a

febrile UTI. The flow charts below illustrate the procedures for treatment failure among these participants. Figure 10.1 outlines procedures for these participants who have a febrile UTI in the first year of the study. Figure 10.2 outlines procedures for these participants who have a febrile UTI in the second year of the study.

Figure 10.1

Grade 3 or Higher Photopenia at Baseline
Patients with a febrile UTI in the first year of the study

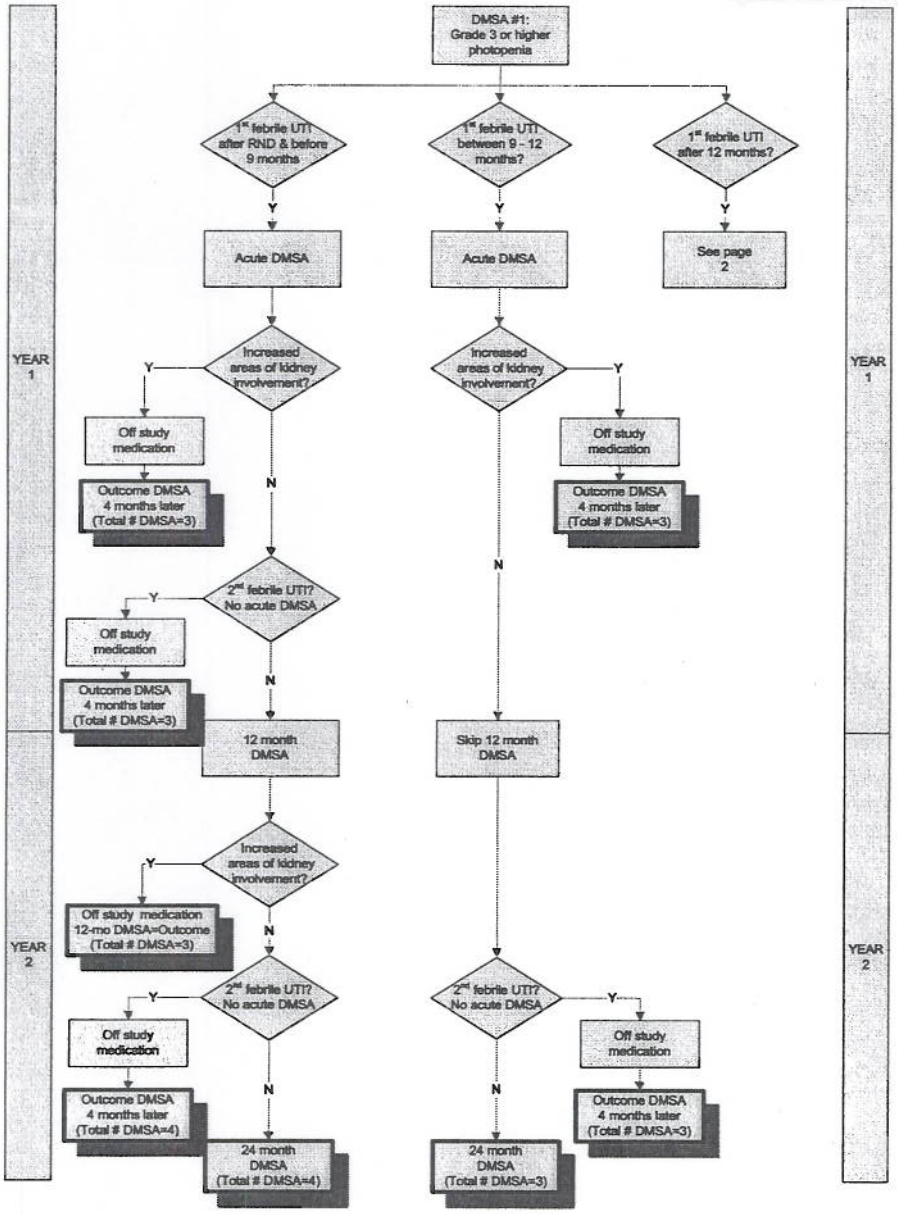
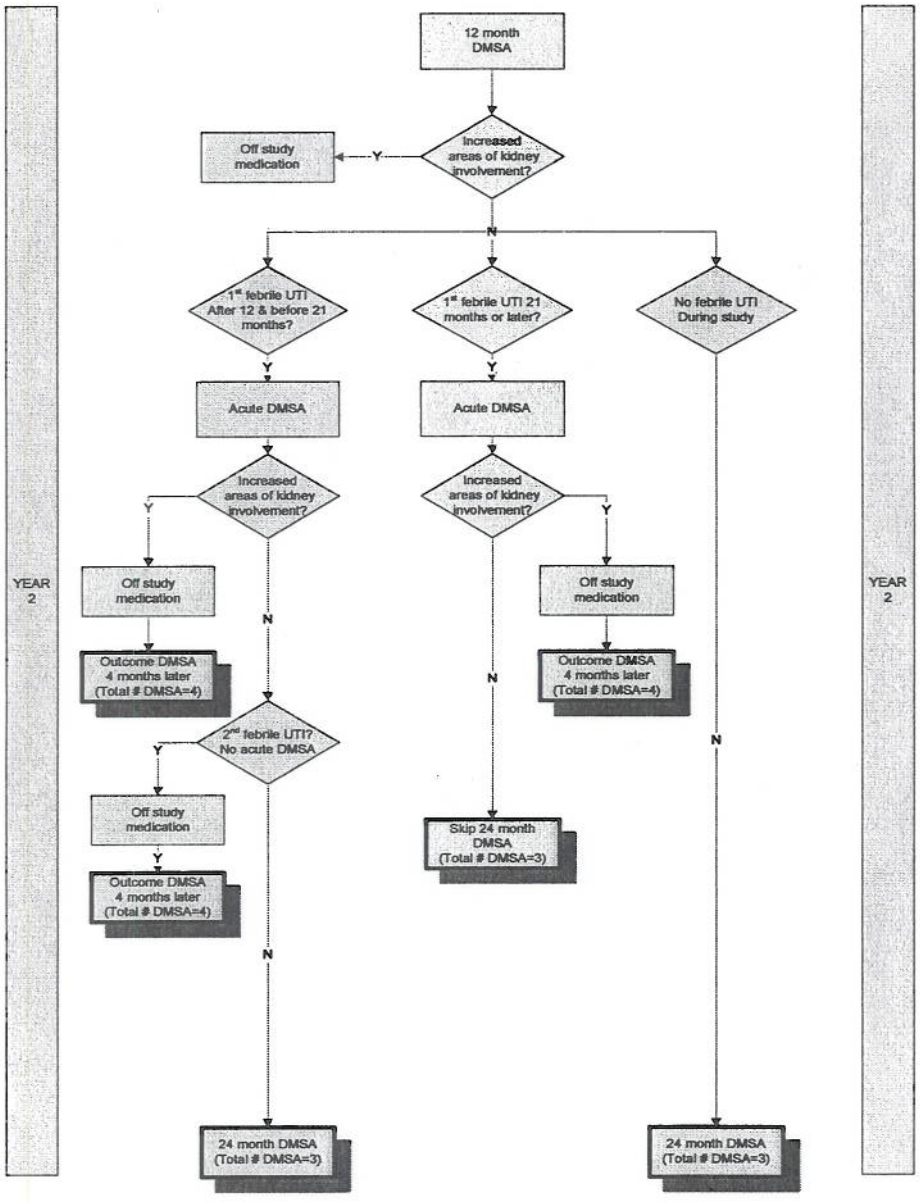


Figure 10.2

Grade 3 or Higher Photopenia at Baseline
Patients without a febrile UTI in the first year of the study



Chapter 11: Quality Assurance and Control

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Chapter 11: Quality Assurance and Control

11.1 Overview

The integrity and ultimate credibility of the study depend on such factors as ensuring adherence to the protocol and study procedures, completion of follow-up information on all participants enrolled, and using quality control measures to establish and maintain high standards for data quality.

Procedures designed to enhance adherence to the protocol and study procedures begin with the training ~~and certification~~ of clinic personnel before participants are enrolled. Once enrollment begins these same measures will continue along with monitoring clinics, operating suitable quality control systems, checking the quality of data collection and the timeliness with which data are received from the clinics, Central Laboratories, Reference Radiology Committee (RRC), and the Clinical Endpoints Committee (CEC).

11.2 Quality Assurance and Control

Quality assurance is considered here as relating to activities to assure quality of data which take place prior to collection of data, while quality control relates more to efforts during the study to monitor the quality of data at identified points in the collection and processing stages.

Quality assurance is the essence of the entire Manual of Procedures (MOP) and includes the following activities:

- Detailed procedures. A clear description of the study design, training, certification, and the various data collection activities provides the blueprint for the study. The MOP is a written reference for study coordinators, and provides documentation of the standard procedures for the study. Procedures for handling the routine, as well as the unexpected, are given.
- Training and updating training. Training is the transfer of the study plans in the Manual of Procedures to the study coordinators and other staff members. Special materials for this purpose will be developed for ~~RIVUR~~CUTIE and will be the basis for initial training and for continuing education during the study.
- Certification. Criteria to examine the adequacy of an individual's training will be established. Individuals meeting these criteria will then be qualified to execute a procedure.

For quality control purposes, ~~RIVUR~~CUTIE data collection and transmission will be monitored by observation and by quantitative assessment using both specific quality control

procedures (e.g., repeated samples for laboratory assays) and statistical analysis of study data. A summary of selected aspects of ~~RIVUR~~CUTIE quality control follows:

How are the CUTIE sites monitored? Will there ever be site visits?

- **Protocol adherence:** Periodic monitoring visits will be made to each site to review adherence to ~~RIVUR~~CUTIE recruitment and data collection procedures. Feedback and general recommendations for improvements will be provided. These visits also provide an opportunity for clinical staff to discuss questions, concerns, and suggestions with the DCC.

- **Quantitative monitoring, clinical sites:** A sample of data collected will be audited to assure that reported trial data are accurate, complete, and verifiable from source documents.

- **Quantitative monitoring, laboratory:** Random repeat measurements will be used to evaluate laboratory blood samples. Duplicate blood samples will be obtained in tandem with approximately 5% of the specimens collected for the study. These samples will be processed, shipped and stored in the same way as regular samples. The laboratory will be blinded to the identity of the duplicate samples and will run assays on them in the same way as for other samples. The DCC will then produce statistical analyses of the repeatability of the results.

- **Quantitative monitoring, radiology image readings:** All ultrasound, VCUG and DMSA scans used in the study are read by at least two reference radiologists. Results will be compared at the DCC and discrepancies will be adjudicated by the reference radiologists. For inter-reader QC, The DCC will select randomly selected scans for repeat readings by the reference radiologists.

- **Quantitative monitoring, Clinical Endpoints Committee:** Study endpoints will be ascertained by at least two members of the CEC independently. Results will be compared by the DCC and discrepancies will be adjudicated by the CEC.

- **Reporting results:** Two aspects of reporting quality control monitoring should be emphasized. First, the results must be timely. When remedial action is required, reporting must be prompt so that a return to an acceptable level of performance is not delayed. Second, the reporting format must be easily understood.

- **Action on results:** With conscientious and trained staff, quality control reports provide an opportunity to praise a job well done. On the other hand, a poor performance is the basis for remedial action. Depending upon past performance, the amount of error, and, taking due account of personal circumstance, the appropriate action may be a simple discussion to encourage a better performance. Re-training may also be appropriate at times.

11.3 Training

11.3.1 Training of Clinical Center Staff

Each new coordinator ~~will~~ should attend ~~central~~ training at the DCC soon after starting with the ~~RIVUR~~CUTIE study. Continued investment in quality data during the study will be made by periodic refresher training sessions which review the protocol and update personnel on any changes which may have occurred.

Certification of study personnel is an essential aspect of effective quality assurance in ~~RIVUR~~CUTIE. After attending a central training or being trained at the local clinic by another centrally-trained coordinator, and meeting all certification requirements, the coordinator is considered certified. Areas of training essential for certification include ~~randomization~~ enrollment procedures, ~~drug handling and accountability,~~ specimen collection and processing, adverse event reporting, endpoints ascertainment and learning the data management system. The DCC will monitor the study data collection to ensure that staff performs only those functions for which they are certified . To protect the quality of the study results, data will not be collected by non-certified personnel.

~~In order to maintain proper collection of data despite potential for personnel changes over the long term follow-up period, the DCC is responsible for establishing and providing the requisite minimum criteria and training and ensuring continued adherence to standards.~~

11.3.2 Training of Reference Radiology Committee (RRC)

Each reference radiologist will participate in telephone training with the DCC to familiarize themselves with the study radiology MOP chapter, associated forms, and the Data Management System (DMS) for radiology forms and adjudication data entry. ~~A pilot study will be conducted by the sites prior to their initiating study randomization, to ensure uniformity in reading and technique of radiographic images. This study will also have an MOP and telephone training.~~ The pilot study used for RIVUR training will be applied to the CUTIE Study.

11.3.3 Training of Clinical Endpoints Committee (CEC)

The ~~UTI Endpoints Committee~~UTI Endpoints Committee (?) will participate in a training session with the DCC to familiarize themselves with the study MOP, endpoints adjudication process, data collection forms, and the Data Management System (DMS).

11.4 Clinic Monitoring

~~There are three major concepts in the RIVUR approach to clinic monitoring:~~

~~Firstly,~~ Celinic staff is encouraged to contact the DCC for an immediate answer to an operational question or for help in obtaining clarification of a particular situation. For questions of a clinical nature, and those the DCC is unable to answer, the DCC will consult

the Clinical Management Committee. For each clinic, a primary Study Coordinator is identified. Each site has a Principal Investigator who has the overall responsibility for the recruitment of participants and management of the study at the clinic.

~~Secondly, site visits are made to individual participating centers by a clinic monitor from the DCC. Monitors will compare data sent to the DCC to that in the clinic and other medical or hospital records, and verify adherence to protocol. There may also be times when a particular clinic demonstrates a need for assistance in following protocol, filling out forms, or documenting events beyond what can be done through telephone conversations~~

~~Thirdly, the DCC will closely monitor clinic recruitment numbers. if recruitment falls below a certain level, appropriate personnel designated by the Executive Committee, such as a team consisting of a urologist or nephrologist, and coordinator from a highly productive center, will be sent to advise on recruitment strategies.~~

11.4.1 Site Visits at the Clinical Sites (?)

The DCC is responsible for assuring that throughout the clinical investigation the Investigators obligations are fulfilled and that the facilities used in the clinical investigation are acceptable. The most effective way to achieve this assurance is to maintain personal contacts between the DCC and the Project Coordinators, Principal Investigators, and clinic staff. The DCC will initiate monitoring visits at least annually at each clinical site in order to assure that:

- the study protocol is followed and implemented in compliance with Good Clinical Practices
- the facilities used by the investigator are acceptable for the purposes of the study.
- changes to the protocol have been approved by the local IRB
- changes to the Manual of Procedures are documented at the site and incorporated into the site procedures
- accurate and complete records are maintained
- the appropriate staff, trained and certified are performing the agreed-upon activities and not delegated to other unspecified staff

11.4.2 Conducting the Monitoring Visit

One month prior to the visit, email the Study Coordinator(s) and the PI a memo to arrange a convenient date for a monitoring visit. Prior to the visit, the site PI and Coordinator will be sent an agenda and a list of participant IDs for data auditing.

Particular issues covered during monitoring visits include:

- adherence to study schedule
- protocol violations and deviations

- enrollment rate
- drop-out rate
- questions or problems experienced by the staff since last visit
- changes in the study staff
- adverse event reporting
- shipment of laboratory specimens
- drug accountability, quantities and storage
- data management issues
- audit of source data
- acceptability of study site facilities and staff

Each monitoring visit will end with a debriefing meeting with the Project Coordinator and Principal Investigator.

11.4.3 Monitoring Visit Reporting

Monitoring visits are completed with a formal written report, distributed to the PI, Coordinator, and the Executive Committee within one month of the visit. The report will summarize the findings during the visit, and highlight all recommendations and action items for both the DCC and the clinical center.

11.5 Data Quality Monitoring

The DCC helps reduce the frequency of errors as much as possible through discussion and training of study procedures and use of data collection instruments before recruitment begins, and through continued review and clarification of the protocol during the study as necessary. The study DMS includes features designed to identify data entry errors at the sites with automated error checks and correction processes. Monthly data management reports of data quality and participant follow-up are prepared and circulated by the DCC. These reports are reviewed to determine which clinics may need to be visited.

11.5.1 Data Check Reports

The DMS includes an automated query system reporting data checks at entry for use in investigating and correcting specific problem items in collected data. The DMS reports provide listings of missing forms, unexpected, and inconsistent data. Additional data quality reports will be run and sent to the sites monthly by the DCC. Follow-up is provided by the DCC to help sites resolve identified problems.

11.5.2 Data Management Reports

Data management reports are compiled and distributed monthly for use in identifying general problem areas in data collection. The standard reports include data on:

- Current study and site recruitment, and recruitment over time

- Screening, randomization and follow-up contacts
  - Timeliness of randomization and follow-up contacts
  - Timeliness of specimen processing and shipping
  - Timeliness of radiographic scan collection and processing
  - Timeliness of endpoints data collection
  - Completeness of forms

- Participant Withdrawal Rate
  - Number of participants who have withdrawn from the study

- Participant Medication Adherence Rate
  - Number of participants whose adherence is less than 75%

11.5.3 Steering Committee Reports

Twice yearly progress reports to the Steering committee will focus on study progress, including status of patient recruitment, quality control issues, and data collection and timeliness. Objective clinic specific analyses of performance will be presented.

11.5.4 Data and Safety Monitoring Reports

Twice yearly DSMB reports (or as required by the DSMB) will be generated by the DCC. While the content of these reports will ultimately be determined by the DSMB requests, the reports will likely consist of four major sections; recruitment and follow-up, side effects and adverse events, efficacy, and data quality. The section on recruitment and follow-up will provide the status of recruitment by clinical centers, including graphs comparing performance goals. It will also detail reasons for withdrawals and non-compliance. The data quality section will aid the committee in evaluating the data collected. It will include information on data completeness and timeliness, rates of questionable data, and protocol violations.

11.6 Laboratory Quality Monitoring

11.6.1 Blood Central Lab QC – Cystatin C and Creatinine

Quality control procedures at the ~~RIVUR~~CUTIE Blood Central Laboratory at Children's Mercy Hospital, Kansas City, MO, are overseen by the Medical Director of the Microbiology program, Dr. Stanley Hellerstein. Their internal quality control program ensures that test results, which are generated by the lab, are accurate, reliable, and reproducible. The goal is accomplished by evaluating the quality of specimens submitted for testing, assessing test performance using appropriate controls, performing instrument function tests and temperature records daily, maintaining written procedures, reviewing personnel performance and technical procedures.

Additional quality control of reagents and media used in testing include:

a. Date all media and reagents upon receipt into the lab, and also specify "date opened".
b. Observe manufacturer's expiration dates and discard materials when outdated.
c. Examine each new batch of media for clarity and color. Media showing signs of dehydration must be discarded.
d. Examine each batch of media for sterility.
e. Perform procedures as described in the technical procedure manual.
f. Assess test performance by testing the appropriate positive and negative control specimens as delineated in the specific procedure.
g. Reference strains are available in the lab.

11.6.2 Anti-microbial Resistance (Rectal Swab) Central Lab QC

1. Quality Oversight and Program Administration:
   The Pathologist-in-Chief has been designated as the Medical Director of the Microbiology program and will be responsible for quality oversight, and the Infectious Diseases Research Lab is under the umbrella of CHP Pathology/Microbiology Department for CAP certification.

2. The purpose of the quality control program is to ensure that test results, which are generated by the lab, are accurate, reliable, and reproducible. The goal is accomplished by evaluating the quality of specimens submitted for testing, assessing test performance using appropriate controls, reviewing personnel performance and technical procedures.

3. Responsibility for the program is as follows:
   Ronald Jaffe, MBBCH , Pathologist-in-Chief
   Jayne Rasmussen, MT(ASCP) MPM, Exec. Director

4. Testing Personnel
   All Infectious Diseases Research personnel will receive training for all testing during their initial orientation. Competencies will be assessed annually thereafter. The Laboratory is responsible for planning and implementing orientation and competency assessment programs in conjunction with nursing education. Records of orientation and competency will be maintained on file in the employee's personnel records and/ or with each respective department's training records. Quality Control is performed by ID Chief Technologist and testing personnel according to procedure unless otherwise noted as performed by laboratory personnel.

5. The Chief Tech reviews records of controls of routine procedures, instrument function tests, and temperature records on a daily basis. Any problems with compliance are addressed immediately, and the Infectious Diseases Lab Director is notified of all problems.

6. The Chief Tech ensures that technical procedures are written in a manner easily understood by technical staff by preparing the written procedures in accordance to the NCCLS document GPA-2.

7. Quality Control of reagents and media:
    - Date all media and reagents upon receipt into the lab, and also specify "date opened".
    - Observe manufacturer's expiration dates and discard materials when outdated.
    - Examine each new batch of media for clarity and color. Media showing signs of dehydration must be discarded.
    - Examine each batch of media fro sterility.
    - Perform procedures as described in the technical procedure manual.
    - Assess test performance by testing the appropriate positive and negative control specimens as delineated in the specific procedure.
    - Reference strains are available in the lab.

11.6.3 External Laboratory QC: Blind Replicate Matching

Blind Replicate Matching (BRM) for the ~~RIVUR~~CUTIE study is a method of quality control to check the precision of methods used by a laboratory analyzing blood and urine samples. This is a '**blind**' check as the lab does not know which samples are being used to test the quality of its work. Essentially, two '**replicate**' tubes/specimens from the same person are labeled with two different IDs so that the lab does not know they are from the same person. The DCC will '**match**' these two IDs from the one participant to compare the results from the analyses.

The study goal is to collect BRM QC on approximately 5% of all vial types for all clinic visits. This means a BRM will be scheduled at approximately every 20 participant clinic visits for each clinic visit type where specimens are collected (i.e., baseline 24 month end-of-study visit).

Each site will be notified periodically by the DCC to collect extra BRM specimens from participants during clinic visits. When notified, the site will collect, process, and ship or store the replicate tubes as well as the regularly collected tubes for that specific visit type.

To minimize participant burden, no more than one BRM blood tube is drawn per participant visit. Therefore, a complete set of BRM tubes for a contact occasion will be comprised of extra specimens collected from multiple participants. However, the same participant can donate an extra tube at different contact occasions (i.e., baseline 24 month end-of-study visits). This extra tube must be the last tube drawn from the participant, and should never require an additional 'stick'. If blood flow is insufficient to fill the BRM tube, a different participant should be selected for collection of the BRM tube. Replicate blood draws will be

used only on participants ≤ 20 lbs where overall blood draws are not to exceed 5 ml, and will only include QC specimens for local and central laboratories. Repository specimens already include multiple aliquot tubes uniquely labeled to account for QC specimens.

The link between a participant's ID and the blind replicate specimen label ID is made through the Specimen Collection and Processing Form (SCP). These forms contain an indicator of whether the sample is a blind replicate duplicate. This is the only way in which quality control duplicates are distinguished from regular samples. In all other respects they are indistinguishable. The Q x Q's for the SCP provide detailed instruction for completing the BRM section of this form.

11.7 Data Management Quality Assurance

The data management system in ~~RIVUR~~CUTIE will provide all the capabilities required for research data management, including: data entry and validation, database updating, database closure, data retrieval, data inventory, security and confidentiality, and archiving.

Chapter 12: Staffing and Training

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Chapter 12: Staffing and Training

12.1 Overview

Certification of study personnel is an essential aspect of effective quality assurance in CUTIE. In order to maintain proper collection of data despite potential for personnel changes over the long-term follow-up period, the Data Coordinating Center (DCC) and the Principal Investigators Committee are jointly responsible for establishing and providing the requisite minimum criteria and training and ensuring continued adherence to standards.

The complexity of the design requires that Project Coordinators be instructed and trained on specific tasks. To protect the quality of the study results, data are to be collected by trained personnel only.

12.2 Project Coordinators

Project Coordinators are responsible for providing the thread of continuity from participant recruitment and enrollment through follow-up, endpoint determination and ultimately study closeout. Coordinators routinely initiate recruitment, conduct interviews and administer questionnaires. Coordinators serve as the liaison with the PIs, the DCC, the Central Laboratories, and the clinical site. They familiarize their physicians and staff with study procedures and implement operational modifications. The Project Coordinator is ultimately responsible for accurate collection of data at the clinic and its transfer to the DCC. The Coordinator is also responsible for overseeing the collection, processing, and shipment of blood and urine samples to the appropriate Central Laboratories and repositories. Therefore, an in-depth knowledge of all aspects of the protocol is required. As such, Project Coordinators attend a training session initially held before recruitment into CUTIE commences.

In general, successful completion of training will result in proficiency in all aspects of study procedures necessary for the collection of data on paper forms and the computerized data management system (DMS) to ensure the accuracy and integrity of the collaborative database. The Project Coordinator must demonstrate proficiency in the use of the DMS during the training to complete the training requirements to enter data and enroll participants on the DMS.

12.3 Training Procedures

Every Project Coordinator must be trained by the DCC. If a clinic has more than one Project Coordinator, then the DCC must train each Project Coordinator.

Once trained, a Project Coordinator can subsequently train additional personnel (auxiliary, back-up) who may perform any or all of specimen collection and processing, data entry, overall data collection or medical records abstraction for endpoint data

collection, provided each person passes the training requirements specific to the activity. In most clinics it is expected that the Project Coordinator will perform all duties relevant to screening and enrollment.

Training of the initial group of Project Coordinators from each site is accomplished by participation in a central training session held by the DCC.

12.4. Training Requirements

At a minimum, training requires a complete reading and familiarization of the CUTIE Manual of Procedures. The central training of Project Coordinators will include presentations and examples of data collection that provide a thorough review of the MOP. In some cases Project Coordinators and auxiliary or back-up personnel may be required to complete a task-specific quiz to verify that all instruction in the Manual of Procedures are understood.

12.4.1 Specimen Collection and Processing Training

Initial training will be based on attendance at RIVUR central training, and demonstration of an acceptable level of proficiency, as indicated on a laboratory quiz of specimen collection and processing administered by the DCC. Clinics utilizing other lab personnel to collect, process and/or ship specimens will be required to give the lab personnel the quiz and submit it to the DCC for evaluation. Phlebotomists who perform the venipuncture **only** are not required to take the laboratory quiz, but are required to receive instructions in CUTIE protocol on the order of draw and handling of the vacutainer tubes. The CUTIE project coordinator is responsible for ensuring adherence to study procedures for specimen collection and processing even if external laboratory personnel are being utilized.

12.4.2 Radiographic Images Collection and Processing Training

Initial training will be based on attendance at CUTIE central training. Project Coordinators who have attended central training may train auxiliary or back-up personnel in proper procedures for collection, processing, and shipping of radiographic images.

12.4.3 Endpoints Ascertainment Training

Initial training will be based on attendance at CUTIE central training.

12.4.4 Data Management System (DMS) Training

Initial training is based on attendance at the central training session. Project Coordinators who have attended central training may train auxiliary or back-up personnel in study data entry procedures. It is expected that only centrally trained Project Coordinators or certified back-up coordinators will perform all data entry relevant to screening and enrollment.

12.5 Coordinator Turnover

If the primary Project Coordinator leaves the study, trained and certified auxiliary back-up personnel (see Section 12.7) can continue to function in their roles. A back-up Coordinator who has completed a central training at the DCC may be designated as the new Project Coordinator with no interruption of study activities. Or, the back-up Coordinator who has been trained by the primary Coordinator may continue all study activities until a new primary Coordinator, or until they are centrally trained by the DCC.

All data collection activities must cease at a site if a new Coordinator has not been trained at a DCC central training, or temporarily by the previous centrally trained Coordinator, and there are no backup or auxiliary trained personnel at that site. The DCC will make every effort to provide emergency training when necessary. Effort should be made to complete such training within 60 days of loss of the primary Project Coordinator.

For clinics with auxiliary personnel, it is recommended that the new Coordinator centrally train as quickly as possible in the areas the previous Coordinator handled exclusively. When the clinic has someone trained for every aspect of the study (combination of new, auxiliary, and back-up), then the clinic can continue study activities.

12.6 Recertification of Coordinators

The need for retraining may be triggered by recommendation of the Executive Committee's review of the data. This recertification may be study-wide or clinic-specific.

12.7 Additional Clinic Personnel

Once training and certification requirements for the Project Coordinators are met, additional personnel may be trained by the Project Coordinator or by the DCC to perform tasks related to the CUTIE study under certain conditions.

Local laboratory personnel may perform specimen collection and processing activities. In this case, the Project Coordinator is still responsible for study protocol and must be certified in specimen collection and processing. Lab technicians must be CUTIE-certified and their initials are entered on the specimen collection form as the person processing the blood.

Data entry personnel may enter data into the DMS from paper forms that have been completed by trained personnel, after training by a DMS-trained Project Coordinator, at a DCC central training, or training during a DCC monitoring visit. These technicians are allowed to enter already collected data into the DMS only. It is expected that only centrally trained Project Coordinators or trained back-up coordinators will perform all data entry relevant to screening, enrollment, and direct data collection and entry into the DMS.

12.8. Reference Radiology Committee (RRC)

The Reference Radiology Committee radiologists are responsible for independently reading, interpreting and adjudicating results of CUTIE renal/bladder ultrasound, VCUG, and DMSA scans. The study endpoints of renal scarring will be comprised from the results of these central readings. The RRC must be knowledgeable of all forms and procedures necessary to read and adjudicate study images, and the computerized data management system.

The RRC will be trained by the DCC by telephone conference call. Training is based on familiarization with the CUTIE Manual of Procedures and attendance at a training session.

Chapter 13: Data Management and Administrative Procedures

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Chapter 13: Data Management and Administrative Procedures

13.1 Overview

This chapter pertains to general guidelines for data collection and processing that will be used throughout the study. It covers topics such as identification of participants, correct usage of contact occasion and sequence numbers, instructions for recording and correcting data collection forms, general data entry guidelines, adding revisions to the Manual of Procedures and to the forms, and general data management guidelines to ensure participant confidentiality, data security accuracy, and accessibility

13.2 Confidentiality

Violating participant confidentiality is regarded as a serious problem. Each Clinical Center's Investigator is responsible for confidentiality of study documents, although this responsibility may be delegated to the Center's Study Coordinator. All study personnel are expected to maintain participant confidentiality.

All study documents should be treated as confidential. Of particular concern is any document that contains both the Study ID Number and the participants name or other personal identification. Clinical data is especially sensitive. No data containing participant personal information will be sent to the DCC. If certain participant data are required to be sent to the DCC, such as records containing details regarding an adverse event or endpoint, personal identifiers must be removed at the clinical center prior to sending to the DCC.

All research data forms and/or paper records must be in a locked cabinet maintained for this purpose when not in use by the study personnel. Records in use must be kept under the supervision of study staff that has been appropriately trained in HIPPA and site specific confidentiality procedures.

Data management procedures for RIVUR were designed with participant confidentiality in mind. All data collection forms are entered and stored at each Clinical Site. Participant name or any other personal identifier will not be entered in the data management system. Participants are identified only by study ID number on all data files at the DCC.

13.3 Participant ID Numbers

ID numbers for participants enrolled into RIVUR are generated at the DCC. Each participant is assigned a unique RIVUR ID number. This ID number is what is used in the studies database to discern participants, no participant names or other identifying information. The clinical center is the only location that maintains the link to any identifying information of the participant. Each site will be given an Excel Spreadsheet of valid Participant ID's for

their own data management purposes, and sheets of Participant ID labels for use on data collection forms, will be provided.

RIVUR ID's will follow the following format:

7 fields:

Field 1-2	Site Identifier
Field 3-6	Participant ID number
Field 7	Check Digit (based on arithmetic algorithm for QC)

The following site identifiers are used:

Site ID	Site Name
AL	University of Alabama
CO	Children's Hospital of Columbus
DC	Children's National Medical Center
GA	Emory University School of Medicine
MA	Children's Hospital of Boston
MD	Johns Hopkins School of Medicine
MI	Wayne Stat University School of Medicine
MO	Children's Mercy Hospital of Kansas City
NY	Women and Children's Hospital of Buffalo
OK	University of Oklahoma
PH	Children's Hospital of Philadelphia
PO	Oregon Health Sciences University
PT	Children's Hospital of Pittsburgh
TO	Hospital for Sick Children, Toronto
TX	Texas Childrens Hospital

RIVUR participant ID numbers are assigned at the time of participant consent.

13.4 ID Labels

The DCC will provide clinical sites with ID labels

13.4.1 Participant ID Labels

Participant ID labels will be provided by the DCC for use on consent forms, data collection forms, and any other source documents (i.e. medical records) to help the site with their data management tasks.

13.4.2 Laboratory Specimen ID Labels

Labels will be provided by the DCC for laboratory specimens shipped to central labs or repositories. These labels will have bar-coding necessary for inventory at the labs, and will also indicate the participant ID number and contact occasion, including sequence number and tube number where appropriate. Refer to Chapter 5: Specimen Collection and Processing for laboratory specimen collection procedures.

13.4.3 Radiographic Image ID Labels

Participant ID labels will be provided by the DCC for CDs and/or films containing study radiographic images. These labels will also indicate the participant ID number, contact occasion, and sequence number associated with the time of data collection. Refer to Chapter 3: Radiographic Images for data collection procedures related to radiographic image collection.

13.4.4 MCID Labels

Each medical care visit (sick visit), regardless of where it occurs (i.e. study clinic, primary physician, hospitalization), made by a participants during the study, is assigned a Medical Care ID Number (MCID) for use on some of the study data collection forms. Labels with these specific ID numbers will be provided by the DCC.

13.5 Paper Forms versus DMS

In RIVUR, the DMS screens are designed to mimic all paper forms. Coordinators can choose to collect study data on paper forms first followed by data entry, or by direct data entry. If paper forms are used, this becomes the original source document for interviews.

13.5.1 Recording Responses

Most of the questions in the RIVUR forms have pre-coded responses. There are a few questions, however, that you must write in a response to the question. Some questions have pre-coded responses as well as an "other" category. If the participant's answer does not fit into a pre-coded answer, you must specify the response. The recording practices below must be followed at all times to assure that the response recorded accurately reflects the participant's answers and to assure the questionnaire data can be converted to machine-readable form.

- You must listen to what the participant says and record/key the appropriate answer if the response satisfies the objective of the question.

- In recording answers to open-ended questions or "other" categories, print/key the response verbatim.
- Use a black ballpoint pen when recording on paper form.
- Record in the white space below the questions any responses "that don't quite fit" in one of the response categories. Your notes will help the analysts in understanding points of confusion, difficulty, etc. When using direct data entry, these notes can be entered as notelogs in the DMS.
- Always print or write legibly when using paper forms.
- If a participant refuses to answer a question, write "refused" in the left margin beside the question and enter equal signs in the response field on the form or on the entry screen.
- A single answer choice code must be circled/keyed in each question to represent the participant's answer, unless the item states you can circle all that apply.

Some of the questions in the RIVUR study ask about recall of events over time. You may assist the participant without violating probing rules by working with him/her on math or pinpointing dates or events. Another way to help pinpoint more accurate information is to ask the participant to think about time of year or season when an event occurred.

13.6 Data Collection Forms

All data collection in RIVUR is documented on data collection forms. RIVUR uses a combination of data collection methods: direct data entry, paper forms followed by data entry, and forms collected on paper only (no entry). All RIVUR data collection forms will also have associated QxQ (question by question) instructions to aid in the data collection process.

13.6.1 Form Structure

The paper forms in RIVUR are designed to correspond almost exactly to the computer screens used for data entry. All items will be listed in the same order on both the paper and screen versions. Most forms are structured as follows:

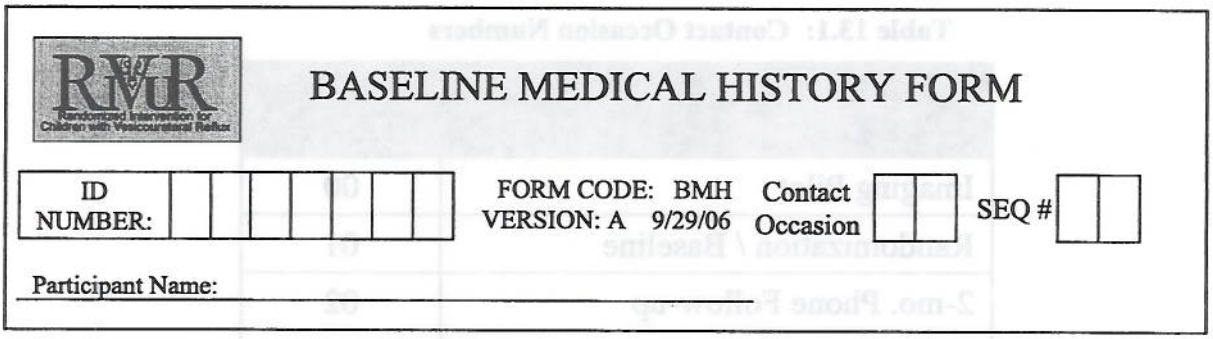
1. Form Title
2. Header Administrative Information
   - Form Code
   - Version Number and Date
   - Participant's ID Number
   - Contact Occasion
   - Sequence Number
   - Participant's Name (this is only an option on paper forms, is not data entered)
   - at the top of each additional page is a space to record the participant's ID, the contact occasion and the sequence number
3. Form Data Items

4. End of Form Administrative Information
    - Date of Examination or Data Collection
    - Method of Data Collection
    - Examiner or Recorder's initials

13.6.2 Header Administrative Data

The information that identifies each form as a unique record in the RIVUR DMS is the key field information contained in the "header" box at the top of all form pages. The following guidelines should be observed in filling out the "header" information located at the top of the each form page.

HEADER EXAMPLE:



13.6.2.1 Participant ID

Preprinted Participant ID labels (Section 13.4.1) should be used in the header of paper forms whenever possible. If the 7-digit ID number is handwritten, care must be taken to make sure the number is very legible for data entry. The first two boxes contain the letters identifying the field center, followed by the 5-digit numeric portion of the ID number.

Example: ID NUMBER:

A	L	1	2	3	4	5

13.6.2.2 Form Code and Version

Form code will be unique for each data collection form in the RIVUR study. Form codes are a 3 character code make up from the forms title. Form versions begin with the letter A, then increment as revisions are made to the data collection forms. Form codes and version are preprinted on all forms.

Form codes and versions are part of the unique identifier of a data record along with ID, contact occasion and sequence number, and are used as part of each data items identifier. For example, question #2 on form Baseline Medical History, version A would be referred to as BMHA2. All data queries and communication from the DCC regarding data items will use this terminology.

It is the responsibility of the site to make certain they are using the appropriate version of each form at all times. For details of the documentation procedures that are designed to facilitate communication to sites about form changes, see Section 13.8.

13.6.2.3 Contact Occasion / Sequence Number / Line Number

13.6.2.3.1 Contact Occasion

The term "Contact Occasion" refers to any protocol specified study contact that occurs while a patient is enrolled in the study. There are 13 protocol scheduled participant contact occasions in RIVUR, and to facilitate data management, these are numbered 01-13. The Imaging Pilot is recorded as contact '00'. These numbers are used in the Data Management System (DMS) and on all paper forms and study documentation to identify and differentiate the various contacts.

Table 13.1: Contact Occasion Numbers

Description	Contact Occasion #
Imaging Pilot	00
Randomization / Baseline	01
2-mo. Phone Follow-up	02
4-mo. Phone Follow-up	03
6-mo. Clinic Follow-up Visit	04
8-mo. Phone Follow-up	05
10-mo. Phone Follow-up	06
12-mo. Clinic Follow-up Visit	07
14-mo. Phone Follow-up	08
16-mo. Phone Follow-up	09
18-mo. Clinic Follow-Up Visit	10
20-mo. Phone Follow-up	11
22-mo. Phone Follow-up	12
24-mo. Clinic Exit Visit	13

Following the first main study protocol contact the randomization and baseline visit (CO 01) there are scheduled study contacts every two months: clinic visit contacts every six months, as well as telephone contacts every two months between the clinic visits. This continues

through the 24-month clinic visit, which is CO 13. CO 13 will be the Exit Visit for the study for most of the participants.

When completing header information fill in the appropriate contact occasion for the form, using leading zeros where necessary. Note: This item may be pre-coded on some forms.

Example: For the Randomization visit the contact occasion should be recorded as:

CONTACT OCCASION: | 0 | 1 |

13.6.2.3.2 Sequence Number

In addition to contact occasion, the sequence number also provides data management information about the timing of data collection activities. Both the contact occasion and sequence number together indicate a contact. Protocol scheduled contacts, numbered in the table above, are always assigned sequence number '00'.

Some data collection forms will be collected independent of protocol scheduled follow-up telephone and clinic contacts, every 2 months. These include reporting of serious adverse events and study endpoints forms such as the Adverse Event Form (AEF), Medical Care Notification Form (MCN), and Medical Care Abstraction Form (MCA).

In situations when data are collected on events that occur between the scheduled study contacts, corresponding data should be labeled according to the most recent regularly scheduled contact occasion preceding the event, and the Seq # should be incremented. For example, if on the 2-month telephone call (CO 02) you discover that the participant was hospitalized once during the previous month, meaning the hospitalization occurred between the randomization visit (CO 01) and the 2-month phone call (CO 02), the corresponding Medical Care Abstraction Form for that hospitalization would be labeled with CO 01, Sequence Number 02 (See Table 13.2 below).

Table 13.2: Sequence Number Usage

Contact Description	Date of Contact	Contact Occasion #	Sequence #
Randomization	08/29/2006	01	00
→ Hospitalization	**9/5/2006**	**01**	**01**
2-month telephone call	10/30/2006	02	00
4-month telephone call	12/29/2006	03	00
6-month clinic visit	02/29/2006	04	00

Even if the coordinator is unable to complete the Medical Care Abstraction form for a hospitalization *or* wasn't informed about it until the 4 month telephone call, the contact

occasion would remain CO 01 because the hospitalization occurred between the 01 and 02 contact occasion dates.

Incrementing sequence numbers allows you to track multiple unscheduled events that occur between scheduled study contacts. For example, in Table 13.3 below there are two different medical care visits that occurred between COs 04 and 05; that is, between the 4-month telephone call and the 6-month clinic visit. The CO for both hospitalizations is 04, and the sequence numbers are 02 and 03 respectively, thereby giving each event its own unique identity.

Table 13.3: Sequence Number Increment Usage

Contact Description	Date of Contact	Contact Occasion #	Sequence #
Randomization	08/29/2006	01	00
2-month telephone call	10/30/2006	02	00
4-month telephone call	12/29/2006	03	00
→ Doctor Visit	**01/09/2006**	**03**	**01**
→ Doctor Visit	**02/11/2006**	**03**	**02**
6-month clinic visit	02/29/2006	04	00

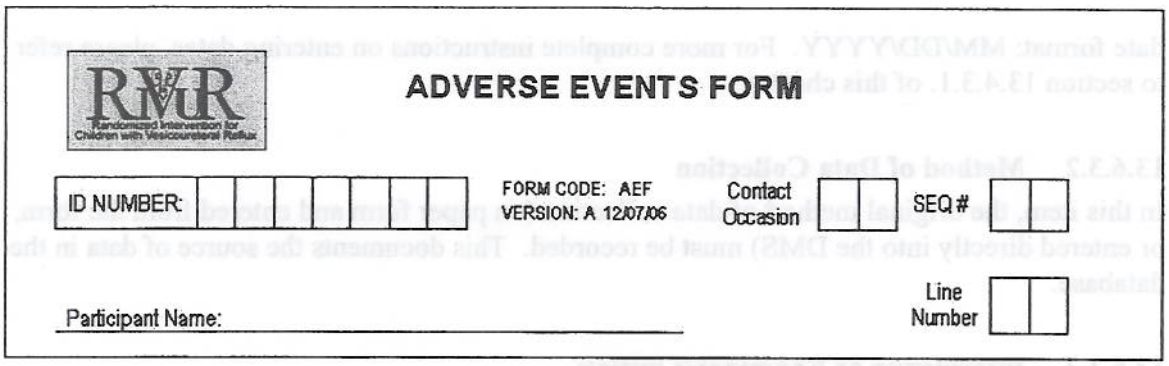
When completing header information fill in the appropriate sequence number for the form, using leading zeros where necessary. Note: This item may be pre-coded on some forms.

Example: For the second Doctor Visit that occurred after CO 03, but before CO 04, the sequence number should be recorded as:

SEQUENCE NUMBER: | 0 | 2 |

13.6.2.3.3 Line Number

Together, both the contact and sequence number indicate a point in time. There are some forms that may be collected more than once at the same point in time. These are distinguished by line numbers. For example, there may be 3 AEF forms reporting different side effects or events all occurring at the same point in time (CO# and SEQ#). See header for AEF form below with space for Line Number.



These multiple forms are all entered into the DMS under the same CO# and SEQ# using the DMS feature referred to as 'Multi-Line'. The DMS assigns the actual Line Number in the order the forms are entered. If you are collecting data on paper forms, you must verify that the Line Number reported on the paper form is the same that is assigned in the DMS.

Refer to the DMS User's Guide for specific instructions on data entry of multi-line forms.

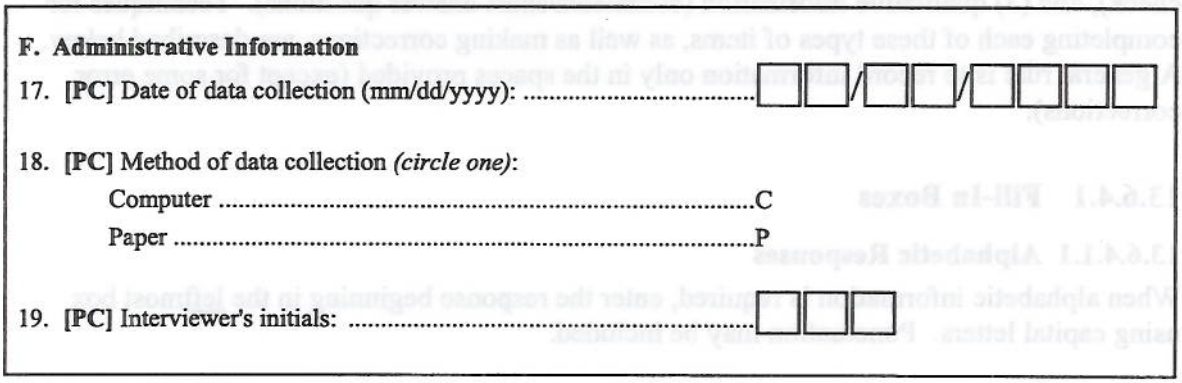
13.6.2.4 Participant Name

This item appears on the paper forms only, and serves as another way for clinic staff to link data collection forms to participant records. Record the participant's full name in the blank provided. The participants name is not entered into the study DMS. A participant's name should never be included on any materials that are sent to the DCC, or be in the studies database.

13.6.3 End of Form Administrative Data

At the end of each form, there is a section titled "Administrative Information." This section provides information regarding when, how, and who is responsible for the data collected on each form, and must be completed for every form.

EXAMPLE:



13.6.3.1 Date of Data Collection

For this item, record the date that the data was collected. This date may not be the date of data entry if data was collected on paper forms first. The RIVUR DMS system uses the U.S.

date format: MM/DD/YYYY. For more complete instructions on entering dates, please refer to section 13.4.3.1. of this chapter.

13.6.3.2 Method of Data Collection

In this item, the original method of data collection (on paper form and entered from the form, or entered directly into the DMS) must be recorded. This documents the source of data in the database.

13.6.3.3 Interviewer or Examiner's initials

The interviewer's initials will be the first, middle, and last initials of the staff person who originally collected the data. If someone does not have a middle initial, leave this field blank. To distinguish between two staff members who have the same initials, one of them should consistently use either their first or last initial as the middle initial.

13.6.4 General Instructions for Recording and Correcting Responses

Review each form and its instructions prior to use. Verify that you are using the appropriate form by checking its 3 letter form code, version, and date, all located in the lower left corner of the page. Each unique form type will have specific instructions for filling out that form in the Procedures Manual. Be familiar with the instructions in the Procedures Manual before attempting to complete a form.

When completing official study paper forms, use black ballpoint pen. Print all text responses legibly; do not use cursive writing. Do not attempt to correct errors on paper forms by using correction fluid or erasers at any time. Data collection forms need to maintain the history of data recorded in the event of an audit. Carefully proofread each page of data for legibility, accuracy, and completeness prior to transferring the form to the data entry staff.

All items fall into one of three main categories: (1) "fill ins", (2) multiple-choice (circle or check), and (3) qualitative information (comments/short-answer questions). Techniques for completing each of these types of items, as well as making corrections, are described below. A general rule is to record information only in the spaces provided (except for some error corrections).

13.6.4.1 Fill-In Boxes

13.6.4.1.1 Alphabetic Responses

When alphabetic information is required, enter the response beginning in the leftmost box using capital letters. Punctuation may be included.

For example: If the name of the investigator who authorized randomization is Bob O-Reilly, then you would enter:

Eligibility Criteria reviewed and randomization authorized by (name of investigator):

B	O	B		O	'	R	E	I	L	L	Y												

If the response contains more characters than there are boxes, beginning with the first character enter as many characters as there are boxes, then enter the remaining data on the form either next to the boxes or directly under, in such a way that anyone entering the data will know that this is a continuation of the response. When this is entered into the DMS, when you run out of field space in the DMS add a "notelog" with the complete information Refer to Chapter 14: Data Management for instructions on data entry of notelogs.

For example: If the name of the investigator who authorized randomization is Stephanie Jones-Hobgoodnotting, then you would enter:

Eligibility Criteria reviewed and randomization authorized by (name of investigator):

S	T	E	P	H	A	N	I	E		J	O	N	E	S	-	H	O	B	G	O	O	N	O	T

(enter the final T-I-N-G into a notelog)

13.6.4.1.2 Numeric Responses

Whenever numerical responses are required, enter the number so that the last digit appears in the rightmost box. Enter leading zeros where necessary to fill all boxes. (This does not apply to the address section or to any item which combines alphabetic and numeric information. Such items should be treated as alphabetic.)

For example: If the participant's diastolic blood pressure is 96, it should be coded as:

Diastolic BP:

0	9	6

It is possible that numeric fields could have a pre-printed number of decimal places. In this case, the QxQ instructions will specify the number of decimal places to be recorded. Instructions on how to round values to the expected number of decimal places are found in the QxQ instructions. When necessary, enter trailing zeros to fill the requested number of places to the right of the decimal point. Leading zeros may be needed so that all boxes to the left of the decimal are also filled.

For example: If a participant's temperature is 99.0°F, then it should be entered as:

Temperature:

0	9	9	.	0

13.6.4.1.3 Dates

In most cases when dates are recorded, slashes ("/") are to be used as the separator characters for month, day, and year. While these are pre-printed on the paper forms, they are **not** pre-printed in the DMS response fields and must be entered along with the numbers of the date. RIVUR uses the U.S. order for recording dates (month/day/year) in the following format: MM/DD/YYYY. The QxQ instructions may also contain information on how to handle

partial dates. When necessary, use leading zeros within each date unit (month or day or year) so that each box is filled.

For example: Data collected on April 3, 2005 would be recorded as:

Date of data collection: | 0 | 4 | / | 0 | 3 | / | 2 | 0 | 0 | 5 |

13.6.4.1.4 Time

RIVUR usually records time using a 24-hour clock. When necessary, use leading zeros within each time unit (hour or minute) so that each box is filled. Note that midnight is recorded as 2400, and noon is recorded as 1200.

For example: If a participant was contacted at 1:45 PM, then it would be entered as

Time of contact: | 1 | 3 | | 4 | 5 |

13.6.4.1.5 Fill-In Boxes: Correcting Mistakes

To correct mistakes in the DMS, simply log onto the Web DMS in change mode and correct the affected fields. For complete instructions on correcting data in the DMS, please refer to chapter 14 of this manual.

On paper forms, if a number or letter is entered incorrectly, mark through the incorrect entry with an "X". Code the correct entry clearly above the original incorrect entry. The person making the corrections should initial the correction, using his/her first, middle and last initials, and record the date of the correction.

For example: If the participant's systolic blood pressure was actually 130, but was incorrectly entered:

Systolic: | 1 | 3 | 9 |

The correction would look like:

0 BAB 06/05/2002

Systolic: | 1 | 3 | ~~9~~ |

If a mistake is made, corrected, and then it is discovered that the correction is incorrect, make a second correction as shown below:

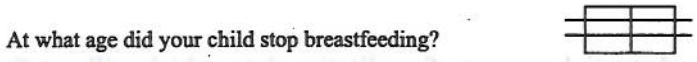
13.6.4.1.6 Fill In Boxes: Unknown or Not Applicable Information

In the DMS, if a data item is not applicable, then the item will automatically be skipped. For example: If you entered 'N' for the question, "Was your child ever breastfed," then you will not be prompted to answer the question "At what age did your child stop breastfeeding." (Please see "Skip Patterns" section later in this chapter.) If you are prompted for a data item in the DMS and the answer is applicable, but unknown, then leave the item blank unless otherwise instructed in the QxQs.

For paper forms, if an item *does not apply* to the participant being interviewed, and there is no clear skip pattern, then simply leave it **blank**. For example, on the Participant Contact Form there are spaces to provide multiple phone numbers for a participant. If the participant does not have an "other" phone number, then simply leave it blank and go on to the next question. Similarly, if the form provides spaces for three measurements, but only two are taken, the third space is left blank.

If the item *does apply*, but the response is unknown, mark through the box(es) with two horizontal lines (like long equal signs).

For example: During the Baseline Medical History interview, the parent guardian indicated that the child was breastfed at one time, but does not recall at what age the child stopped, and is unable to provide an estimate. The item "At what age did your child stop breastfeeding" *does apply* because it has been established that the participant was previously breastfed, but the answer to this question is *not known*. In this case, the response on the paper form would look like:



13.6.4.2 Multiple Choice: Recording Information

In this type of question several alternatives are given for the answer, each having a corresponding letter. When it is decided which alternative is most appropriate, circle the corresponding letter in the space provided. Always circle one letter only.

Example: If the participant indicates that they were told by their physician that their renal graft function has deteriorated, the response would look like:

Have you been told by your physician that your renal graft function has deteriorated? Y Yes

(N) No

13.6.4.2.1 Multiple Choice: Correcting Mistakes

To correct mistakes in the DMS, simply log onto the Web DMS in change mode and correct the affected fields. For complete instructions on correcting data in the DMS, please refer to chapter 14 of this manual.

On paper forms, if a response is coded incorrectly, mark through the incorrectly coded response with an "X" and circle the correct response. The person making the corrections should initial the correction, using his/her first, middle and last initials, and record the date of the correction.

Example 1: The actual response is No, but Y was circled incorrectly. The correction looks like:

BAB 06/05/2002

(X) Yes

(N) No

Example 2: If a mistake is made, corrected, and then it is discovered that the correction is incorrect, make a second correction as shown below:

BAB 06/06/2002 BAB 06/05/2002

(Y) (X) Yes

(X) No

13.6.4.3 Qualitative Data

Some forms need to collect a substantial amount of qualitative data, which will not fit in pre-designated boxes. An example of this would be the description of a serious adverse event. These responses should be as short and succinct as possible. Handwriting on paper form should be written carefully and legibly. Many of these items will be entered into the DMS as notelogs, which will allow variable length fields. Some will be items that were triggered to automatically pop up the notelog feature, others may require the user to open the notelog feature.

In addition to qualitative responses requiring entry via notelogs, all handwritten comments on a paper form, should be entered as a notelog associated with the specific item the comment refers.

Refer to the DMS User's Guide regarding notelog data entry.

13.6.4.4 Skip Patterns and "Go to" Boxes

Skip patterns occur in many multiple choice type items. Here, if a certain response is selected, it is necessary to skip over one or more items to the next applicable item. This is indicated by an arrow from the response which necessitates a skip, to a box containing a "go to" statement. If that response is selected, the next item to be entered is the one indicated in the box. If the other response is selected, always proceed to the next item unless otherwise directed in the QxQ.

Example: 18. Is this a Telephone Contact? Y Yes → [Go to Item 20]

N No

In this case, if the response is "Yes", skip to item 20. If the response is "No", proceed to the next question, item 19.

Occasionally, a skip pattern will occur in a fill-in type item. In those instances, specific instructions are provided on the form and QxQ. Again, if the skip criteria are not satisfied, continue with the next item.

A few items may trigger a skip regardless of the response. For these, follow the instructions on the form.

13.6.5 Problem Clarification and Data Queries

The DMS is programmed to automatically query out of range values during the data entry process. In addition, the DMS has a query resolution feature. Programmed edits regarding data values within or across forms will generate queries in the DMS. There may also be additional query from the DCC regarding data values discovered to be questionable during analysis or other more complicated data checks. These queries will be sent electronically to the data manager, forms will be identified by header information, data items will be identified by question numbers, the original response will be indicated, and the reason for query will be described. Corrections to these queries are also made through the DMS.

13.6.6 Permanently Missing Contacts

Follow-up and tracking of participants is critical in a randomized trail. A missed contact is never interpreted as a participant's withdrawal. In this type of study a participant is never considered withdrawn from the study, even when refusing contact. In the event that a participant's parent/guardian refuses consent for continued contact then the Consent Tracking Form (CTF) must be modified to stop any data queries from the DCC regarding expected forms not received. In the event that a protocol scheduled contact is missed, an FUP form for the missed Contact Occasion should be completed and noted in Section A of the form, this too will avoid queries for expected forms.

13.7 Data Management

13.7.1 Web Based Data Management

The RIVUR Data Management System [DMS] is a set of programs, which the DCC uses to manage data collected in the RIVUR Clinical Centers. This DMS has been designed for flexibility using World Wide Web systems. It is designed for data entry from paper forms or interactively as data is collected. The system can be used from any computer with a high speed Internet connection. Data entry computers must have Microsoft Internet Explorer 6. The RIVUR DMS User's Guide, Chapter 14 of the RIVUR MOP, provides specific instructions on its use. Username and Passwords to use the system will be provided to each site's Project Coordinator from the DCC in a secure and confidential manner.

The DMS provides several major functions:

- Data Entry: Allows data collection forms to be keyed, edited and updated, locally through the RIVUR internet DMS.
- Randomization: Provides interactive randomization through the RIVUR Web database.
- Data queries: The DMS has a data query and resolution feature that us run by the user.
- Reports: Provides reporting based on study need.

13.7.2 Clinical Center Data Management

The DMS will have numerous reporting programs designed as a tool to help facilitate data management at the sites. The RIVUR DMS reporting systems will generate participant lists, form inventories, scheduling reports, recruitment reports, missing forms reports, query reports, etc to help the field centers with any data management tasks. Requests for additional reports or lists can be made from a field center to the DCC.

Actual scheduling and other managing of participant flow, data collection, and filing of paper source data is the responsibility of the clinical site.

Chapter 14: the DMS User's Guide will contain documentation of the reporting facilities. Information on updates and changes to these reports will be provided through the Numbered Memo communication (Section 13.8.1). As these reports get updated and changed, additional training will occur during the monthly Project Coordinator conference calls.

13.7.3 Laboratory Data Management

Various specimen Collection and Processing Forms will allow tracking of laboratory specimen collection and processing. Additional specimen Shipping and Inventory Logs will also provide a specimen shipping and tracking system.

Refer to Chapter 5: Specimen Collection and Processing of the RIVUR MOP for further details..

13.7.4 Radiographic Images Data Management

Radiographic image Shipping and Inventory Logs will allow tracking of radiographic image collection and mailing.

Refer to Chapter 3: Radiology for detailed procedures regarding radiographic image collection and processing.

13.7.5 Data Management Reporting

The DMS will have numerous reporting programs designed as a tool to help facilitate data management at the sites. Chapter 14: Data Management User's Guide will contain documentation on the DMS reporting facilities. As these reports get updated and changed, training conference calls may be scheduled.

13.7.6 DMS Training and Certification

DMS training will be held in Chapel Hill during the studies central training before the study start. Project Coordinators of each site are required to be present, any site may send additional staff to these trainings.. Those attending may provide additional training to other staff members at their sites. Follow-up conference call training sessions will also be scheduled as needed. As new clinics are brought into the study, or as new Project Coordinator's are hired additional central training sessions will be scheduled as needed. There will also be site monitoring visits throughout the study and some DMS training can occur during these visits as well ,(depending on available time and resources.)

Refer to Chapter 12: Staffing and Training regarding the studies staffing and training requirements.

13.8 Official Study Documents

Current versions of all study documents, protocol, data collection forms, chapters of the MOP, user's guides, and other important documents are available on the study website at http://www.cscc.unc.edu/rivur/. These require the appropriate username and password for entry into the documents section. Each document exists as a PDF file in order to retain any necessary formatting.

IMPORTANT: Versions of these documents that are designated as usable in the field will have been sent to each study site in an official RIVUR Study Documents Notebook. One notebook will be provided to each Project Coordinator. Section 13.8.3 describes the process of communicating and verifying receipt of communication on modifications and updates of documents.

13.8.1 Numbered Memos:

The DCC will routinely send various emails or memos that are numbered and identified as "Numbered Memos". These memos are considered official documents and are to be stored at the back of the documents notebook. Updated information regarding the protocol, forms, MOP chapters, QxQ's, and other documents being used in the field will be sent to the centers as Numbered Memos. Numbered Memos will be sent to all RIVUR Project Coordinators and Steering Committee members. It is the site's Coordinator's responsibility to make sure this notification goes to all RIVUR staff at each site that is affected. Each Project Coordinator must send email confirmation of receipt of the Numbered Memo to Dana Edelen NEED ADDRESS.

The numbered memo will instruct the recipient to print from the Web the updated version and place this into the Site's Manual of Procedures Notebook (Project Coordinator's notebook), replacing the older version. Numbered memos should be stored at the back of each binder form back to front with the most recent memo on top. Each site should provide archival storage of previous versions of documents according to their Institutional requirements. The DCC will also keep all versions of official documents archived. Only memos that say DCC Memo # should be filed in the Numbered Memos section.

The Project Coordinator's notebook (not the PI's notebook) is considered each site's official documentation. The status of this notebook is monitored during any site monitoring visits.

13.8.2 Adding Revisions to the Manual of Procedures

All forms, MOP pages/chapters, MOP table of contents and QXQ's are saved in PDF format and are located on the RIVUR website at http://www.rivur.net. The DCC will send each Study Coordinator numbered memos via email regarding revisions to the MOP.

13.8.3 Instructions for Adding New/Corrected Materials

Forms:
Any new or corrected form will be available to print from the website. Forms should be replaced and copied for immediate use. Email confirmation to the DCC (Dana Edelen dana.edelen@mail.cscc.unc.edu) when the revised forms are downloaded.

Manual:
The revised pages/chapters of the FAVORIT Manual of Procedures should be printed from the website and filed immediately in the MOP binder. Email confirmation to the DCC (Dana Edelen dana.edelen@mail.cscc.unc.edu) when the revised pages/chapters are downloaded.

QXQ's:
Any new or corrected QXQ will be available to print from the website. They should be printed and filed immediately together with the appropriate form in the MOP binder. Email confirmation to the DCC (Dana Edelen email address dana.edelen@mail.cscc.unc.edu) when the new QXQ's are downloaded.

13.8.4 Instructions for Outdated Materials:

Take all outdated pages of the MOP, forms and QXQ's, attach to a copy of the appropriate numbered memo, and place in a permanent, chronological "Archive Manual" binder or file folder.

13.8.5 General Filing Instructions

All randomized participants should have either a binder or file folder filed in chronological order by participant ID. If the center prefers to file by last name there should be a cross-reference available with the corresponding ID number. It is important for centers to be able to communicate effectively with DCC by the participants' ID number. Data queries sent to the sites from the DCC will only identify participant ID numbers. **Remember, before sending any hospital records or forms to DCC, blind all personal information pertaining to the participant.**

Forms used for participants should be separated with index tab dividers or colored paper by the contact occasion/sequence #. This organization will expedite your response to data queries and facilitate site monitoring. For numerous hospitalizations, file by contact occasion and then by sequence number (example 1st hospitalization CO: 05, seq 01, 2nd hospitalization CO: 05, seq 02). Forms should be filed consistently with each contact occasion.

Each clinical site is responsible for assuring that participant study data is stored in a secure location that meets participant confidentiality requirements and assures the necessary masking of treatment assignment among the staff.

File all non-randomized participant forms together in a file.

13.9 Techniques for Conducting the Questionnaire Interviews

13.9.1 Introduction

This section stresses the importance of interviewer-participant's perceptions and introduces the concept of the interview as a one-sided passing of information. The interviewer's most important technique is analytic listening. Listening affects the interviewer-participant relationship as well as the content of the interview. There are several hallmark barriers to listening that every skilled interviewer recognizes:

- interviewer expectations
- interviewer fatigue and/or boredom
- interviewer anxiety
- interviewer impulsiveness

- note taking
- tendency to evaluate
- distractions and interruptions

Although no one interviewer experiences every one of these during any one interview, four remedies to the above barriers to listening are often suggested:

- Be prepared; lack of organization is in and of itself a distraction.
- Involve yourself in the interaction.
- Concentrate on listening to what is being said and what you are recording.
- Integrate the messages; does a response require further clarification or does it present contradiction to a previous statement?

When completing paper questionnaire forms, the recording practices below must be followed at all times. This will assure that the response recorded accurately reflects the participant's answers, and that the questionnaire data can be easily entered into the DMS.

- You must listen to what the participant says and record the appropriate answer if the response satisfies the objective of the question.
- In recording answers to open-ended questions or "other" categories, print the response verbatim.
- Use a black ballpoint pen.
- Record in the white space below the questions any responses "that don't quite fit" in one of the response categories. Your notes will help the analysts in understanding points of confusion, difficulty, etc. Notes on paper forms can be entered as notelogs in the DMS.
- Print or write legibly.
- If a participant refuses to answer a question, write "refused" in the left margin beside the question and enter equal signs in the response field.
- A single answer choice code must be circled in each question to represent the participant's answer, unless the item states you can circle all that apply.

Some of the questions in the RIVUR study ask about recall of events over time. You may assist the participant without violating probing rules by working with him/her on math or pinpointing dates or events. Another way to help pinpoint more accurate information is to ask the participant to think about time of year or season when an event occurred.

13.9.2 Response Styles

A structured interview, as is proposed here may sound like a conversation, but it is in fact not a conversation. It is rather one-sided passing of information. The interviewer can help to

maintain control of the interview by controlling his/her response style. It should be recognized that a large portion of the impression that the participant has of the interviewer is based on the interviewer's voice and the manner with which the interviewer responds to the participant's comments. Along this line, the interviewer may **never** respond in an **evaluative or judgmental manner**. Such a response would indicate that the interviewer has made a judgment of the relative goodness, appropriateness, effectiveness, or rightness of the participant's statement. Thus if the participant says, "I think I must have had 3 or 4 strokes before my wife made me call the doctor," the interviewer should not say, "Well, maybe you should have called him sooner." That type of response suggests that the participant has made an error which may, in fact, have resulted in causing his current medical problems. It should be borne in mind that the interviewer, by announcing affiliation with a medical study and conducting the interview in the hospital or clinic, has invested in him/herself the potential in the participant's mind for being part of the treatment staff, and this divestment of the role of caregiver while conducting the interview can be particularly difficult when the interviewer is at other times an active member of the institution's health care delivery system. Confronted with such a situation of answering an evaluative statement on the part of the interviewer, the participant may wish to terminate the interview.

A second type of response style is **interpretative** which might also be called teaching or preaching. An interpretative response is one which indicates that the interviewer's intent is to teach. This type of response is also not appropriate, as it would detract from the verbatim type of narrative that is required here. For instance, if the participant says that he/she experienced a sudden episode of right arm paralysis that went away after several hours, the interviewer should not say, "You probably had a TIA." We are interested in the participant's impression of what was happening, and not in the interviewer's impression. We are, further, interested in the facts that lead the participant to make an interpretative judgment, not in the interpretation itself.

A third response style that would be inappropriate would be **interrupting or sentence completion**. However slowly the participant is speaking, putting words in the participant's mouth, or not allowing the participant to finish thoughts will, in general, alter the information which the participant is attempting to give. However, long hesitations may be bridged by asking appropriate questions.

Appropriate response styles are discussed below. First, **supportive remarks** are ones that indicate that the intent of the interviewer is to reassure, to pacify, or to reduce the intensity of the participant's feelings. The general clucking, or understanding murmuring, are both supportive type remarks. Another, in response to the participant experiencing a sudden loss of sight might be, "That must have been difficult for you. Can you tell me what happened next?" Such remarks may help the participant to feel that the interviewer is still listening, is feeling empathy, and yet may not intrude on the flow of the conversation interview. Other supportive remarks, such as "Yes, my grandfather recently had a stroke, and it was a similar situation" probably will detract from the interview. Such remarks will certainly lengthen the interview in that the participant will probably want to go through the interviewer's grandfather's situation as well. While the interview with the participant may eventually be

completed, discussion of the interviewer's personal situation is non-productive and irrelevant.

The second appropriate response style is the **nondirective or understanding response** style. This is more frequently used when an interview includes a third person, acting as informant when the participant is experiencing a communication deficit. Should the participant's informant say, "My husband went into the bathroom, and then I heard a crash," the interviewer might respond by saying "I see." This is the general idea again of understanding murmuring or clucking. The interviewer also might repeat what the participant has just said, "Your husband went into the bathroom and you heard a noise." This may prompt the participant to elaborate.

A third appropriate response style which will be necessary in both types of interview is **probing**, although probing will be more restricted when the interviewer cannot speak directly with the participant who is reporting an event. A probe is a response that indicates that the interviewer's intent is to seek further information, to provoke further discussion along a certain line, to question the participant. Direct probes will be specific questions about details of what the participant has said. The interviewer is cautioned to limit the probes to those provided in this chapter. Another type of probe would be a request for clarification. Thus the interviewer might say, "I didn't understand that fully" or "Would you please elaborate on that?" Additional information on appropriate probing will be discussed in a later section.

13.9.3 Tempo of the Interview

Since the interview is focused on the participant, it must proceed at the pace which the participant, not the interviewer, finds comfortable. A deliberate, careful participant will be irritated and confused by having questions delivered too rapidly. It is well to remember that the participant is doing you a favor. If you go faster than s/he wants to, you give the impression that you are not really interested in what the answer is. If you go too slowly for a quick, decisive person, you will lose his/her interest, and s/he will be bored. Establishing the right tempo takes practice and observation.

13.9.4 Communication Traps

All interviewers, even those with a great deal of previous interviewing experience, should be aware of common communication problems in order to avoid them when conducting interviews. Some of these faults in communication are:

1. Anticipating and answering questions with the interviewer's own thoughts rather than the participant's. Thinking ahead and mentally finishing the participant's sentences will interfere with the interviewer's understanding of what the participant is really saying.
2. The interviewer hearing what he/she expects to hear rather than what is really being told to them. The interviewer must keep listening attentively.

3. Being drawn into the conversation personally by the participant. When dealing with an emotional participant there might be a tendency on the part of some participants to draw the interviewer into a discussion of his/her own similar experiences. The interviewer must guard against being made the "star" of the interview rather than the interview being centered on the participant. If this does occur, the interview will be longer than necessary or will fail to get the information needed.

13.9.5 Probing

Many participants will begin to pour out a good deal of information with little prompting. Others will have to be encouraged to give the information needed. With both types of participants, subsidiary questions may be needed to direct the conversation and elicit more complete answers.

A probe is a neutral, non-leading question designed to start an individual talking or to channel the conversation toward the information that is desired. Probes are used when an answer is unclear, incomplete, appears to be untrue or inconsistent, or when no response is given. There are precautions: do not interrupt the participant; do not give the impression that you are not listening; do not paraphrase the participant's words, and do not suggest an answer.

With the above caveats in mind, there are several types of probes which could be used effectively in the interview. Neutral probes include:

1. Silence: Silence is the most valuable probe. Many people react to silence. The interviewer who waits quietly and patiently will find a few seconds of silence is sufficient and the participant will often clarify a previously inadequate answer.

2. Repeating the question or a previous answer: If the answer given was irrelevant, be sure to repeat the question as stated in the questionnaire. In some cases, it will be necessary to remind the participant of the frame of reference, i.e., to remind him/her of a previous answer which led you to ask the current question.

3. Encouragement: "I see, un huh, hmm!" are effective. Without interrupting, the interviewer lets the participant know that s/he is still there and listening. Avoid comments like "okay" and "all right", which can be misinterpreted as being judgmental.

4. Definition: When asked by the participant for a definition of a term in the question, the interviewer can use the probes suggested in the instructions.

5. Clarification: Explanations to clear up an ambiguity: Could you explain that a little more?," "I'm sorry I didn't understand that." (This puts the onus of being unclear onto the interviewer rather than on the participant.)

6. Channeling is used with talkative individuals to focus on one aspect at a time "Tell me more about _____."

7. Continuation keeps the conversation moving with a non-verbal individual "And then what happened?", "What did you/he/she do then?"

8. Completion makes sure that all information on a participant is given before moving onto another area "Anything else?", "Can you tell me more about that?"

If the participant does not understand the question after one reading:

1. Repeat the question as worded, more carefully and slowly this time. (Often initial confusion is due to the interviewer's having read the questions too fast the first time. This extra time allows the participant to think and may be all that is needed for him/her to understand the question.)

2. Precede the (repeated) questions with a statement like, "Let me repeat the question....", so that the participant will understand that you are attempting to clarify the question for him/her.

If the participant still does not understand the question or asks you about its meaning:

1. Repeat the question exactly as worded.
2. Read the question slowly.
3. Precede the question with a phrase like, "The question I need to ask you..." so that again, the participant will not feel that you are simply impatiently reading the question as a command for his/her prompt answer.

Do not leave a probe dangling. Always record the response to a probe even if it's only "No" or "That's all I can think of."

Always cross-reference. When you probe to clarify a response, always indicate which response you are clarifying. There will be times when a participant will say something ambiguous and continue talking. When you probe to clarify the ambiguous response, indicate the question being clarified.

Examples of Neutral Probes:

- How do you mean that?
- I would like your opinion....
- Can you tell me more about this?
- Can you give me an example? Or, for example?
- Can you explain that in a little more detail?
- How are you using the term....?

- How is that?
- If you had to choose, which would you say?
- What else can you tell me about that?

Chapter 14: CUTIE Data Management System User's Guide

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Chapter 14: CUTIE Data Management System User's Guide

Data for the CUTIE Study is entered via the RIVUR Data Management System [DMS]. This User's Guide contains instructions pertinent to the operation of version 1.0 of the CUTIE Data Management System [DMS]. When the DMS is updated to a later version, the Coordinating Center will send update memos. Please refer to the update memos and any available addenda to this guide for complete instructions. In the event of significant changes to the DMS, a complete updated User's Guide will accompany the update.

14.1 CUTIE DMS

The CUTIE DMS is accessible over the World Wide Web. It will run on any computer with a high speed Internet connection. The computer must have Microsoft Internet Explorer 6 installed.

To access the system, open IE6.

Go to the URL https://dms.cscc.unc.edu/RIVUR.

14.2 Overview of Data Collection

In the course of performing a study, data for a number of participants must be collected at various times for later analysis. These data items are organized into groups of logically related information called forms or form types. Each form is then assigned a brief mnemonic code for easy reference, i.e. "BDF" for Baseline Demographics Form, "FUP" for Follow-up Form, etc.

It is sometimes necessary to change the content of a form during the course of a study. To allow for such changes, we assign a version letter to each form. The initial version is "A", and subsequent versions follow alphabetically. Thus, "BDFA" refers to "Baseline Demographics Form, Version A."

Since each form is be collected one or more times for each study participant, extra information is included to uniquely identify each recorded instance, or record, of a form. These identifiers, or key fields, include Study ID (ID) and Visit #. The ID is a unique code assigned to the participant. The Visit specifies the contact at which the form was collected. If more than one record is collected for a participant at a given Visit, a unique Form Sequence number must be assigned to each record.

We refer to all data items on a form as questions and assign a question number to each item. Typical question numbers may include both letters and numbers, e.g. 1, 2, 3a, 3b, etc.

Data items may be initially collected on paper forms and subsequently entered (or keyed) into an electronic database for statistical analysis. Or data may be recorded directly on the screen without being transcribed from a paper form.

A database consists of tables of data, arranged into fields and records. Each table (form) can store many records (instances of a form), each containing a set of values for every field (question) in the table.

Each table in the database must have a unique name for identification, as must each field in a table. We assign each table's name to be the form and version of the source of its data. We assign each field's name to be the name of its table and the question number of the source of its data. Hence, the table containing data for form BDF, version A, is named BDFA and contains fields named BDFA1, BDFA2, BDFA3, etc.

Each record in a table is uniquely identified by its set of key fields. Thus, no two records in a table may have the same set of key field values (ID, Form, Visit, Form Sequence).

14.3 DMS Functions

The CUTIE Data Management System [DMS] is a set of programs which manage data collected in the CUTIE Clinical Centers.

The DMS provides several major functions:

- Data Entry: Allows data to be keyed, edited and updated.
- Data Transfer: Allows laboratory data to be sent to the CUTIE Coordinating Center for inclusion in a consolidated database
- Enrollment: Determines patient eligibility.
- Reports: Provides eligibility reports, counts of records entered by form type, missing forms reports, query reports, form prints, etc.
- Query: Runs cross-form and cross field validation checks and generates error reports. Provides a mechanism for query resolution.

14.3.1 User Interface Standards

The DMS uses a combination of menus, mouse clicks and a few control keys to control its actions.

14.3.1.1 Keyboard, Mouse and Menus

The DMS uses the keyboard in a conventional way, i.e. the typewriter keys are used to type numbers, letters and symbols.

Items such as fields, menus and Ids and forms from the hierarchical menu can be selected using the mouse. To select an item, move the pointer to the item and press the left mouse button once.

Menu items can be selected using the mouse. Some menu options have further choices which are displayed in a pull-down list when the option is selected. Use the up and down arrow keys to move the bar to the desired option and click once.

Some submenu options have shortcut keys which are a combination of the ALT key and a letter, or the CTRL key and a letter. To use the shortcut hold down the ALT or CTRL key and simultaneously press the letter. Specific shortcut keys will be described when the menus are discussed.

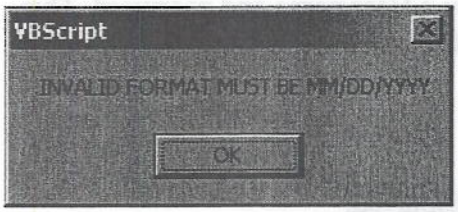
Under some conditions menu options are unavailable. For example if a user does not have delete privileges, the Delete option is not available. Unavailable options are not highlighted and cannot be selected.

14.3.1.2 Lists

Some fields, for example the form field on the ID screen, can be selected from master lists. When the cursor is on the form field, put the cursor on the drop down arrow and click the left mouse button once. To select an item, place the highlighted bar on the item and click on the desired option. The item selected will be put in the field.

14.3.2 Information and Warning Messages

Messages from the DMS display a message box with the OK button:

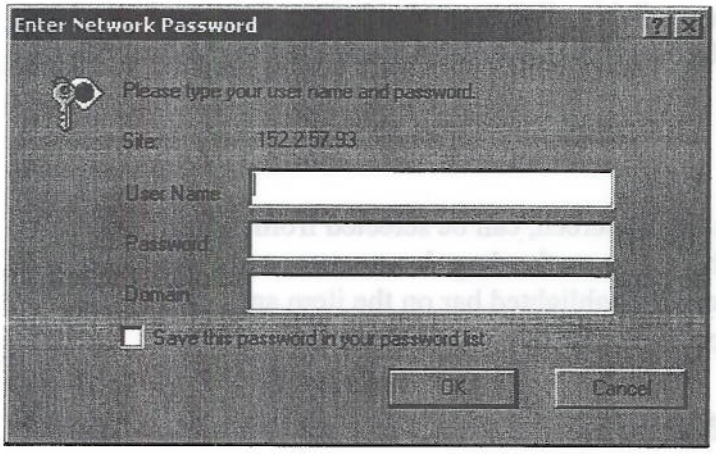


The message remains on screen until you click OK or press Enter.

14.4 Data Entry

Start Internet Explorer 6. Enter the URL: **https://dms.cscc.unc.edu/RIVUR**

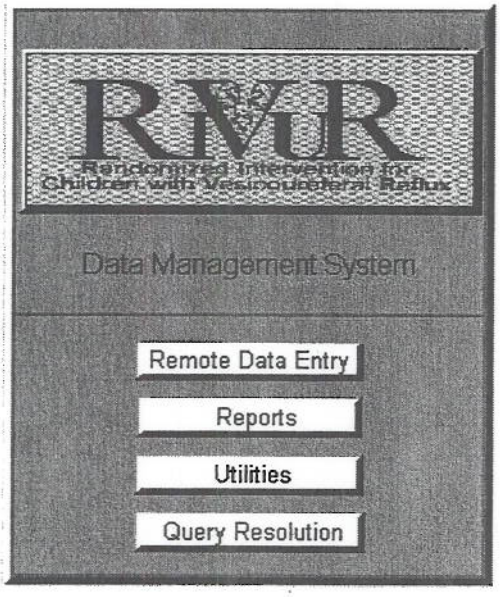
After your browser connects to the site, you will get the following login screen.



This Windows login provides the first level of security for accessing the RIVUR/CUTIE Data Management System. The Coordinating Center will assign you a User name and password. This username and password will be identical to the one for RIVUR.

14.4.1 System Menu

After you successfully log in to Windows, the DMS menu is displayed:

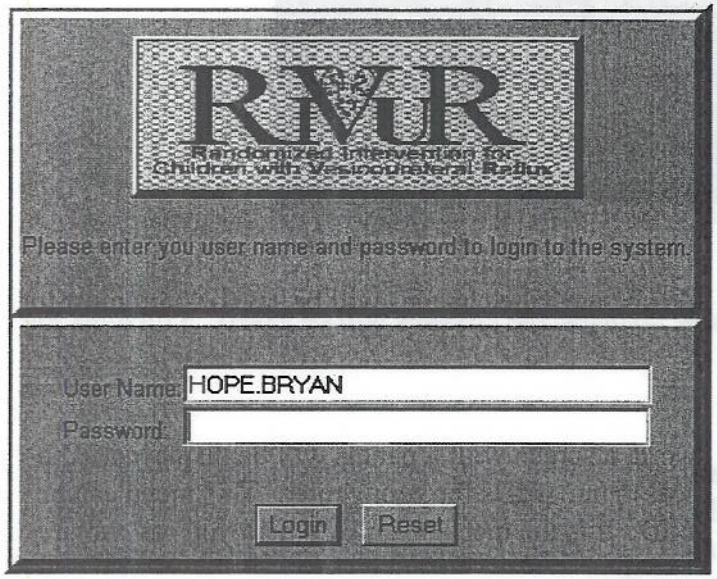


'Remote Data Entry' is available when the computer you are using is connected to the internet. The Remote data entry option writes data directly to the CUTIE study database at the coordinating center.

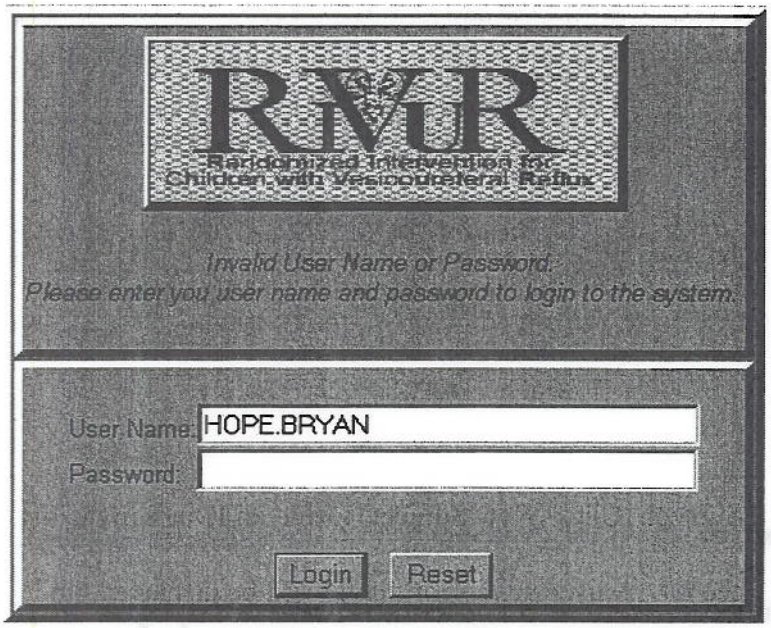
To remove the IE tools bars and thus have more area on which to display data entry screens, press F11. This toggles the tool bars on and off.

14.4.2 Login and Timeout

The second level of ID and password security require you to enter another ID and password. This username and password must be different than your RIVUR login information. The data coordinator at each site will assign these IDs and passwords.

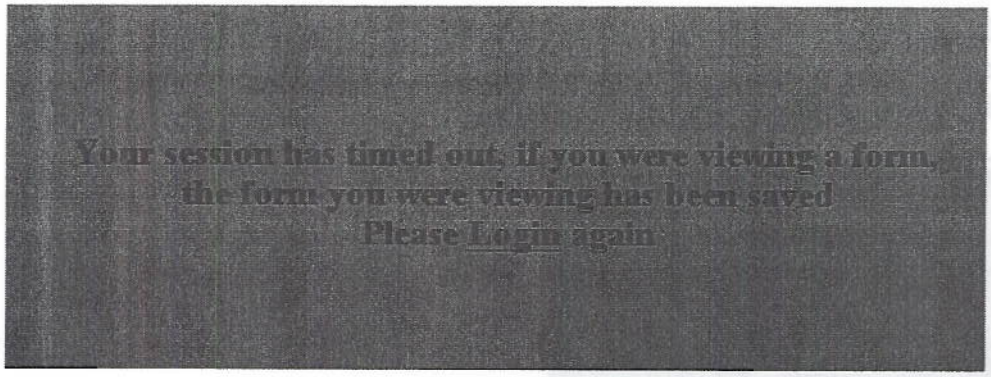


Enter your user name and password. Then click the 'Login' button. If the user name or password is invalid you will see the following screen:



After the DMS is started, leaving it unattended presents a security problem because an unauthorized person could view confidential data. If no contact is made between the browser

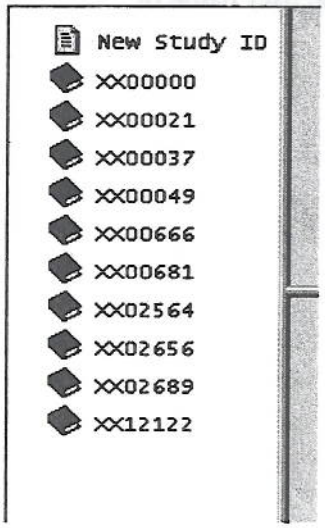
(running on your computer) and the server (saving a form, requesting an existing form) for 10 minutes, the system will time out. If the system times out, you see the following screen:



If you were working on a form and had made changes, the changes will be saved. You must log in again.

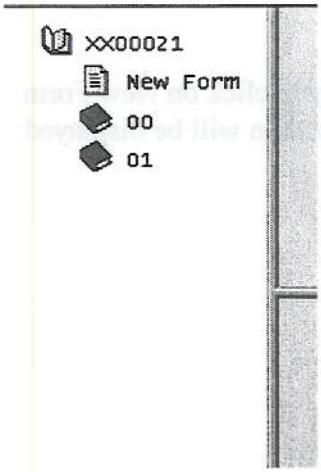
14.4.3 Entering Data

After you enter a valid user name and password, a screen with 3 panels will be displayed. The panel or frame on left displays the hierarchical menu of IDs for your center. This menu can be expanded to display all forms entered for an ID. It is the mechanism by which you can move from one form to another or from one ID to another.



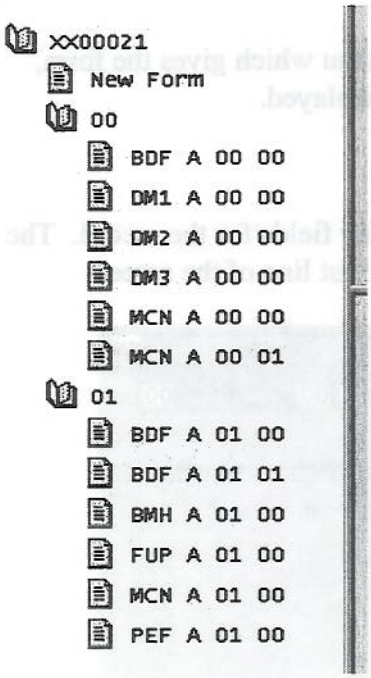
The first selection in the menu is 'New Subject. Click 'New Subject' to add an ID not in the list.

To display all forms for an ID, click on the ID. A list of visits for the ID will be displayed. In the example below, the user clicked on ID XX00021. All visits which have at least one form are listed.



Click on 'New Form' to add a form for a visit which currently has no forms.

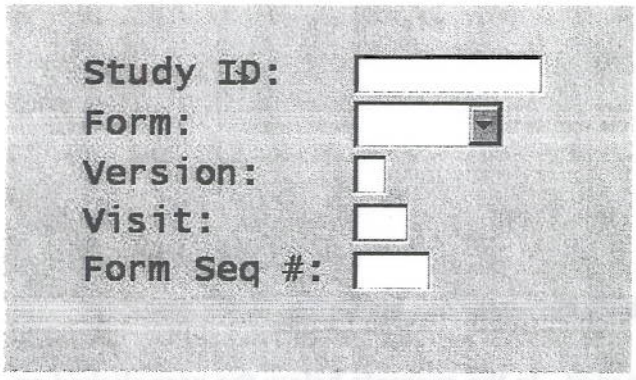
Click on a visit to show all forms entered for that visit. In the example below the user clicked on visit 00. The form mnemonic, version, visit and sequence number are shown in columns. In the example below, Subject XX00021 has 6 forms at visit 00 – BDF, DM1, DM2, DM3 and 2 MCN forms. The form sequence numbers – 00 and 01 – are listed beside visit 00. Subject XX00021 has 6 forms at visit 01.



To return to the complete list of Ids, click on the ID at the top of the menu.

14.4.4 Adding a New Form

When you click New Subject to add the first form for a Subject or when you click on New Form to add the first form for a visit or a new form to an existing visit, the ID screen will be displayed:



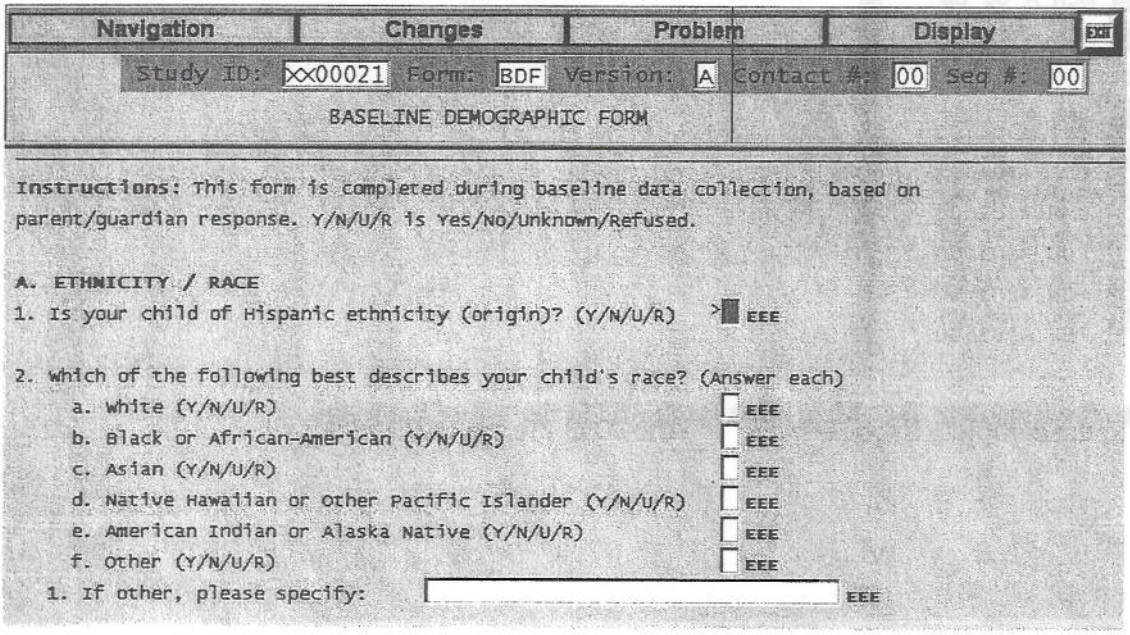
Enter the key fields for the form you are adding. After you enter the last field, a blank form of the type specified will be displayed.

14.4.5 Changing an Existing Form

To change an existing form, click on the row in the hierarchical menu which gives the form, version, visit and sequence number. The form with data will be displayed.

14.4.6 Form Entry

When a form is displayed, the top frame of the screen shows the key fields for the record. The cursor is on the first data field of the record. A menu bar fills the first line of the screen.



There are 3 types of entry fields: text boxes, drop down lists and check boxes.

1. Text Boxes: (all fields in example above.) When entering data in text fields, the cursor will move to the next field automatically if the response fills the field. If the response does not fill the field, you must press enter to advance the cursor.

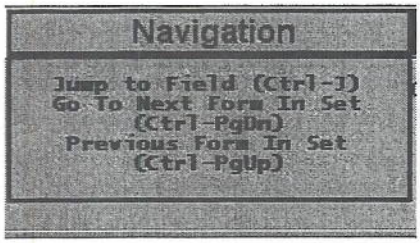
2. Select Lists: (not shown in example above.) To select a response from a drop down list, click on the down arrow on the right end of the response box. A list of valid responses will be displayed. Click once on the appropriate choice. Once you have selected a response, the cursor will advance to the next field.

3. Check Boxes: (not shown in example above.) To choose a check box, click on the box. Clicking once checks the box; a '1' will be stored in the database for a checked box. Clicking again, un-selects the box; a '0' will be stored in the box. If a box is not touched, a missing will be stored in the database.

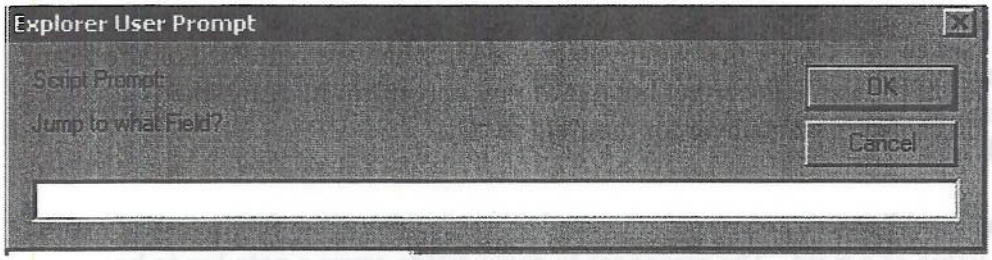
14.4.7 Menu Options

14.4.7.1 Navigation Option

The options under 'Navigation' allow you to 'Jump to Field' or move to the previous or next form in a form set.



Jump to Field allows you to move to a specific question on the form. Selecting this option brings up a menu in which you enter the number of the question to which you want to go:



If you enter an invalid question number you will be alerted.

Jump to Field allows you to go to skipped fields. Jump to field will not let you bypass a must enter (mandatory) field. If you enter a question number which falls after a must enter field which is blank, the cursor instead stops at the must enter field.

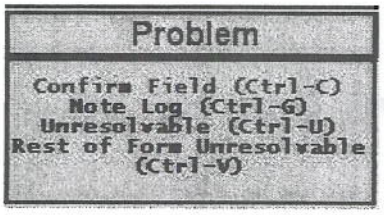
Form sets

Some forms are grouped into 'form sets'. The group is given a form mnemonic and that is the form name entered on the ID screen. Forms in a form set come up in a pre-determined order. When you are entering a form set once you save the first form, you can choose 'Go to Next form in Set' from the Navigation menu or press CTRL+PGDN to move to the next form in the set.

14.4.7.2 Problem Option

As you enter data values into a record, they are edited. Each data field that you enter has an associated status byte vector which stores editing information about the field, such as whether the field is empty, missing, or contains an out-of-range value. The status byte value for an empty field is 'E'. When a valid value is entered, the status byte becomes 'A'. Other status byte values are determined by the user when selecting choices from the Problem option.

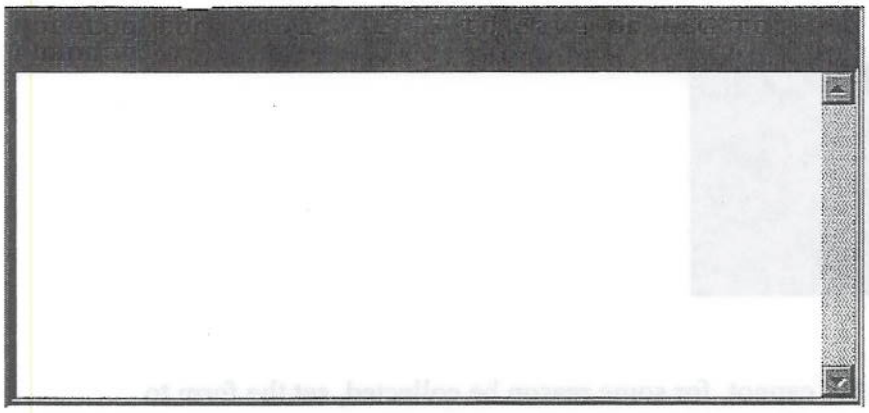
The problem option allows the following choices:



If a value fails an edit, for example if it is out of range or inconsistent with other values, an error window alerts you and gives the valid range or list of valid values:

Press OK to clear the message. Check that what you entered is what was collected on the form. If not, retype the value. If the value is correct but out of range, confirm it. using the first choice of Problem Option. This sets the status byte for the field to 'C'.

Some fields may require additional comments. A note log can hold a value for an 'other' option or a comment on the value of a field. The responses to some fields cause a note log to be displayed automatically. You can also create a note log manually by selecting 'Note Log' from the Problem Menu. The following screen is displayed:



Enter the text for the note. Press ALT+S to save the note log or press ESC to cancel the note log.

If a field has an associated note log the 3rd status byte changes from 'E' to 'N'.

To delete a note log, open the note log and delete all text. Then press ALT+S to save.

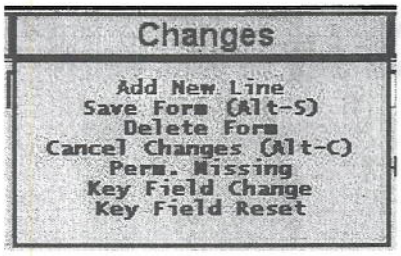
If a value cannot be collected or when the value you did collect is suspicious and should not be used in analysis, you can set the field to Unresolvable. You can also set all remaining fields on a form to Unresolvable.

Unresolvable sets the first status byte to 'U' and, if the field is blank, fills the field with equal signs (==) or for a select list field, sets the value to '= unresolvable'. Note that you can set a field to Unresolvable by keying the equal signs into the field rather than using the Problem menu.

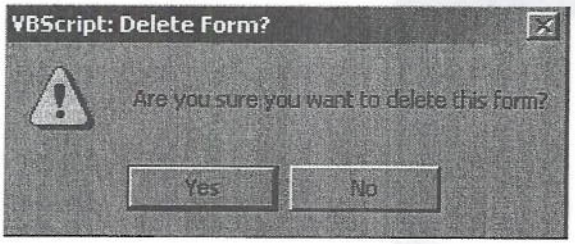
Set rest of form to Unresolvable fills all remaining fields on a form with equal signs and sets their first status bytes to 'U'.

14.4.7.3 Changes Option

The Changes Menu provides options that allow you to save a new form, save changes to an existing form, cancel changes or delete a form or set a form to Permanently Missing.

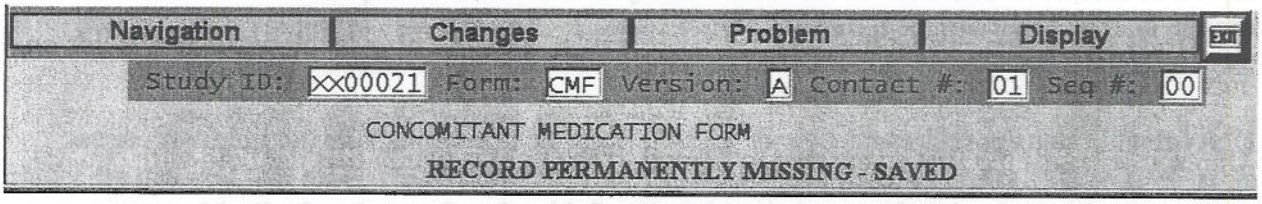


Select **Save** to save the current state of the record to the database.
Select **Cancel** to cancel all changes to an existing record or to cancel the addition of a new record.
Select **Delete** to delete an existing form from the database. You will be prompted:



If a form is expected at a visit but cannot, for some reason be collected, set the form to **'Permanently Missing'** using the 'Perm. Missing' option on the Changes menu. This alerts the coordinating center that you are not able to collect these data. The coordinating center will know not to query you about the record. A record can be set to permanently missing only in Add mode.

When a record is set to permanently missing, the first status bytes for all fields are set to 'P'. When displaying a permanently missing record, the header frame indicates the record is permanently missing.



You cannot save changes to any field.

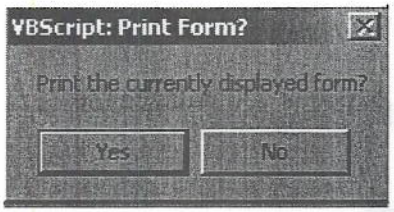
Key fields, fields that uniquely identify a record, can be change by selecting **'Key Field Change'** from the Changes menu. After you select 'Key Field Change' the cursor will be focused on the ID field in the header frame of the screen. You can change the ID, Visit or Form Sequence Number using this option. You cannot change the key fields of a record if a record with the new key fields already exists in the database.

14.4.7.4 Display Option

The display option allows the user to turn off display of the status vectors. The display is turned off only while the current form is displayed. When you display a new form, the status vectors reappear.

14.4.7.5 Print Form

To print a paper copy of a DMS form, display the form on the screen. With the cursor in the body of the form, right click. The following message will be shown:



Choose "Yes" to print.

Print form should be used only when a printer is attached to the DMS computer or laptop

14.4.8 Skips

Some fields are answered conditionally. That is, a certain response to one field can cause subsequent fields to be unnecessary or irrelevant. In the DMS these fields are skipped. After a response is entered into the trigger field, the cursor skips ahead to the next relevant field. Since the cursor is sometimes hard to find after a long skip, the currently active field is identified by a ">" symbol.

You cannot move to a skipped field.
The status bytes of skipped fields are changed to indicate the fields were skipped. The status byte values remain the same but are changed from upper to lower case.

Although the paper version of all forms have been adapted to CUTIE, the electronic version on the DMS has not. There will be several questions that are RIVUR specific, which will need to be skipped. This can be done by entering equal signs (=) until the cursor moves to the next question. Entering "=" for all questions that do not pertain to CUTIE will avoid queries popping up for unanswered questions.

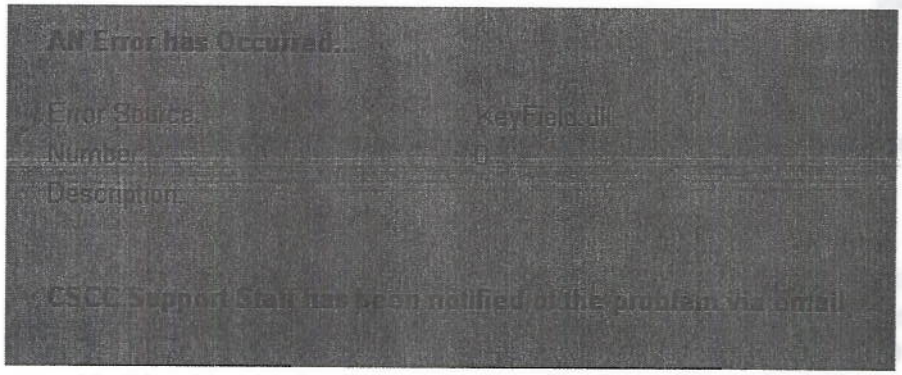
14.4.9 Saving a Form

There are several ways to save a new form or to save changes made to an existing form.

1. Select 'Save Form' from the Changes Menu.
2. Press ALT+S when the cursor is in the data frame section of the screen.
3. Click another item in the Hierarchical Menu.
4. Close the browser by clicking on the "X" in the right corner.
5. Click the 'Exit' button on the menu bar.

14.4.10 Fatal Errors

Occasionally the system might experience a fatal error. When this happens you will see the following screen:

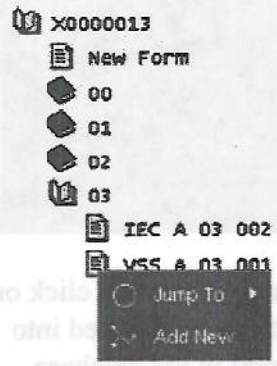


When a fatal error occurs, an email is automatically sent to the DMS staff at the coordinating center. They will work on a solution as soon as possible. You can also call to verify that they received an email. It will not damage the system to go back in and try another task.

14.4.11 Multi-Line Forms

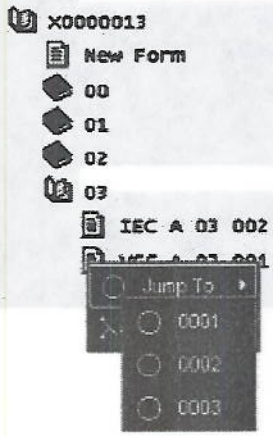
Some forms are arranged with many lines of values for a small set of data items. These **Multi-Line** forms are keyed in much the same way as other forms. To add a new form, enter the key fields on the ID screen. Once the record is displayed, you will notice that only the values of a single line appear on the screen. The line number of the current line is displayed in the **Header Window.** Once you have keyed all values for the line, the line is saved.

To add another line for the same form, **right** click on the **icon of the page** beside the form name in the hierarchical menu. (If you click anywhere else in the hierarchical menu, you will be asked if you want to print the ID list.)



Click on "Add New" from this pop-up. A new set of blank fields will appear for entry and the cursor will move to the first field of the screen. Continue adding new lines until you have added all lines which appear on the form.

You may move from a line to another in a multi-line form by selecting "Jump To" from the pop-up in the hierarchical menu.



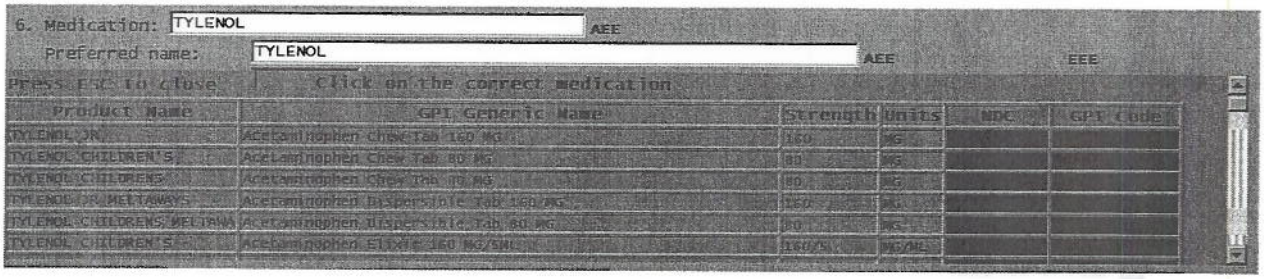
Left click on the line number you want to display.

If you wish to delete a line from the record, use the **Delete form** option on the "Change" menu.

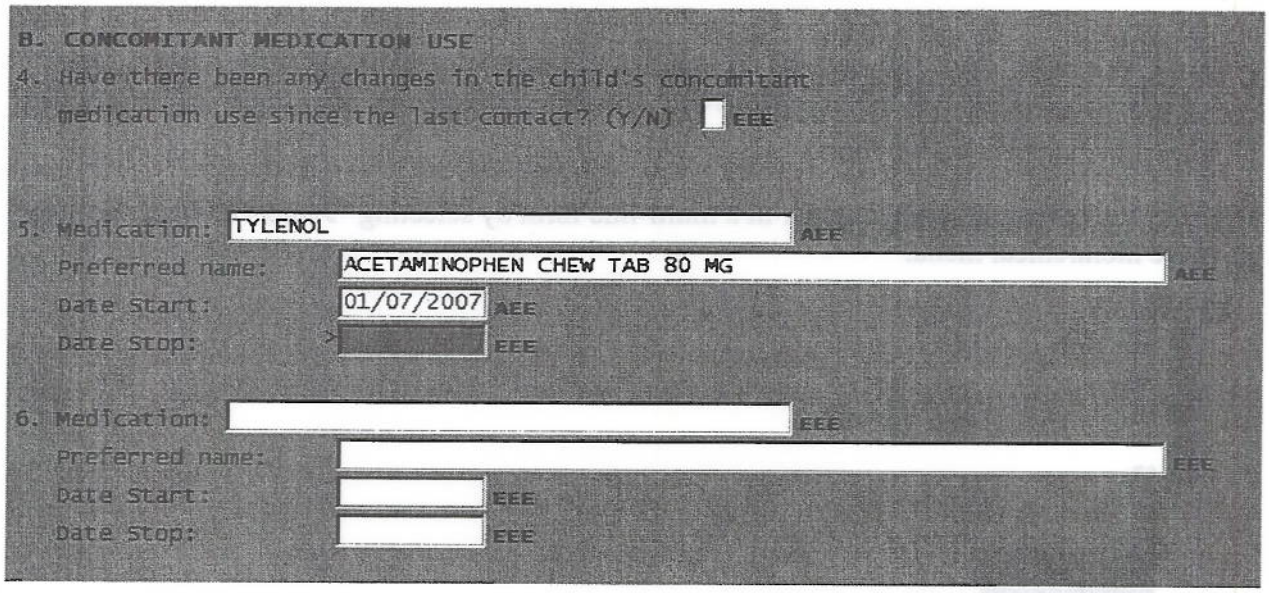
14.4.12 Look-up Fields

Some fields are entered and then coded using a standard coding scheme. Medications and adverse events are both coded by the DMS. On the CMF form, there are sets of fields for recording medication names and the start and stop date for each. To perform the coding, enter the medication name in the field labeled 'Medication'. Enter the same name in the field labeled 'Preferred Name'. When you press Enter after the 'Preferred Name' field, a look-up table will be

displayed with potential matches for the medication. For example, if 'Tylenol' is entered, the following list is displayed:



The list is long so there is a scroll bar on the right. Find the correct medication and then click on the product name or generic name you want. That name will replace what you have typed into the 'Preferred Name' field. The code associated with your selection is stored in the database.



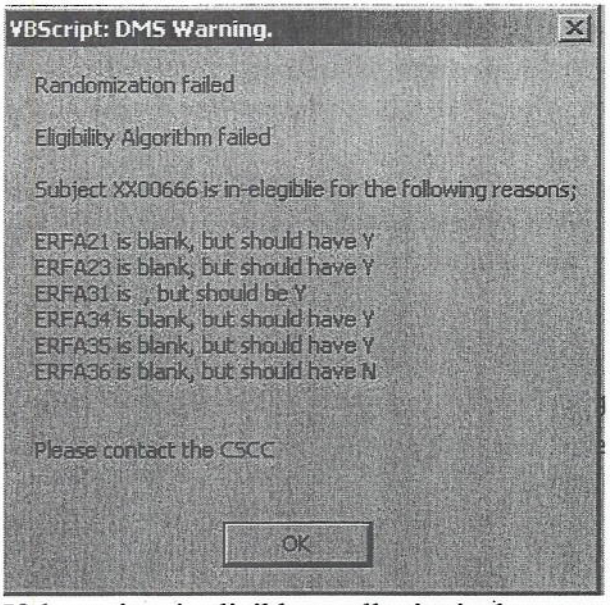
The AEF form has a similar look-up feature for coding Adverse Events.

14.5 Enrollment

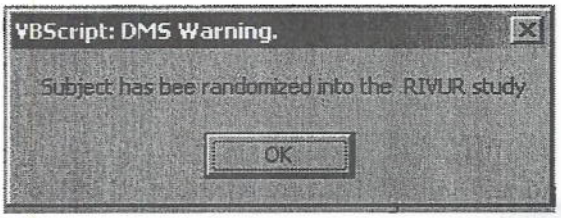
To enroll a patient, select 'Data Entry' and enter an EEF form for the patient. The EEF form must be entered at Visit 01, Form Seq # 01.

The EEF includes questions to determine whether the patient is eligible. After entering eligibility information, you are asked if you want to enroll. If you respond 'Y', the the enrollment program checks the eligibility criteria.

If the patient is ineligible the program warns you:



If the patient is eligible on all criteria the system displays a message that the enrollment was successful.

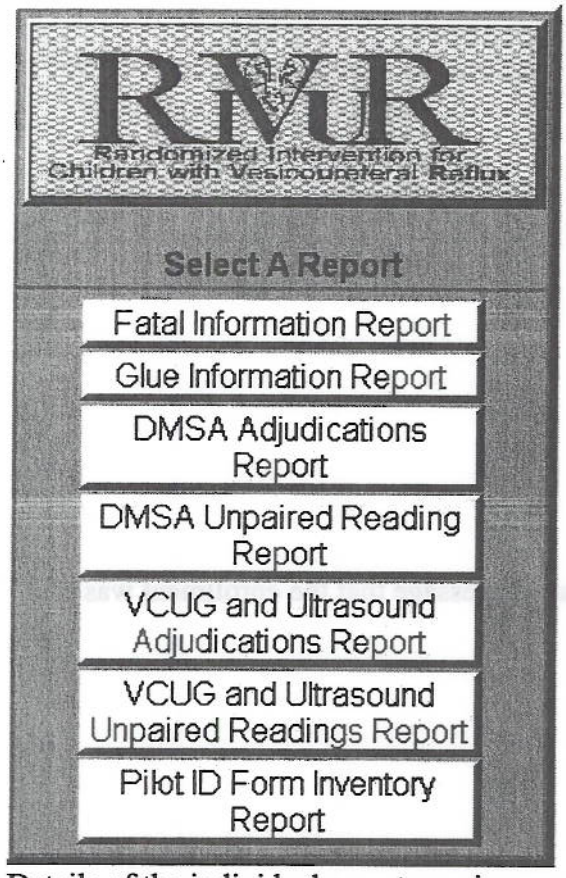


Once a patient is enrolled, you can neither delete the EEF form nor change its values. If you access the form, you are automatically forced into Browse only mode.

14.6 Reports

The CUTIE DMS has several reports including the recruitment and enrollment report and form inventory report.

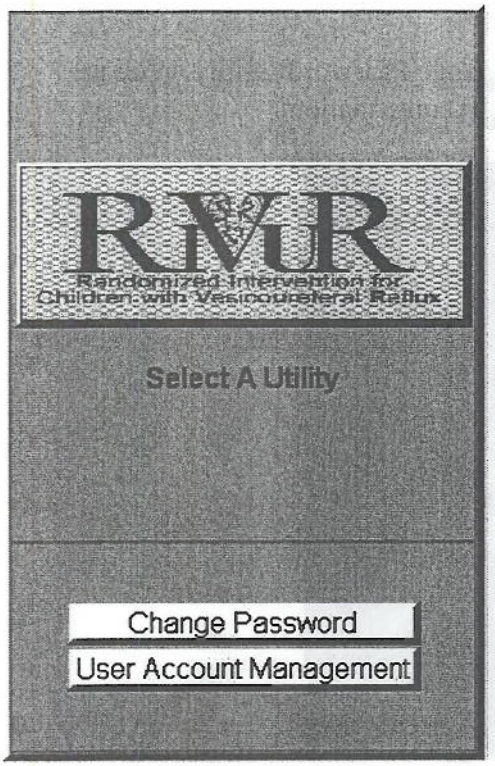
To run reports, choose Reports from the main menu. After you log in with your CUTIE user name and password you get the Report Menu:



Details of the individual reports are in a separate appendix.

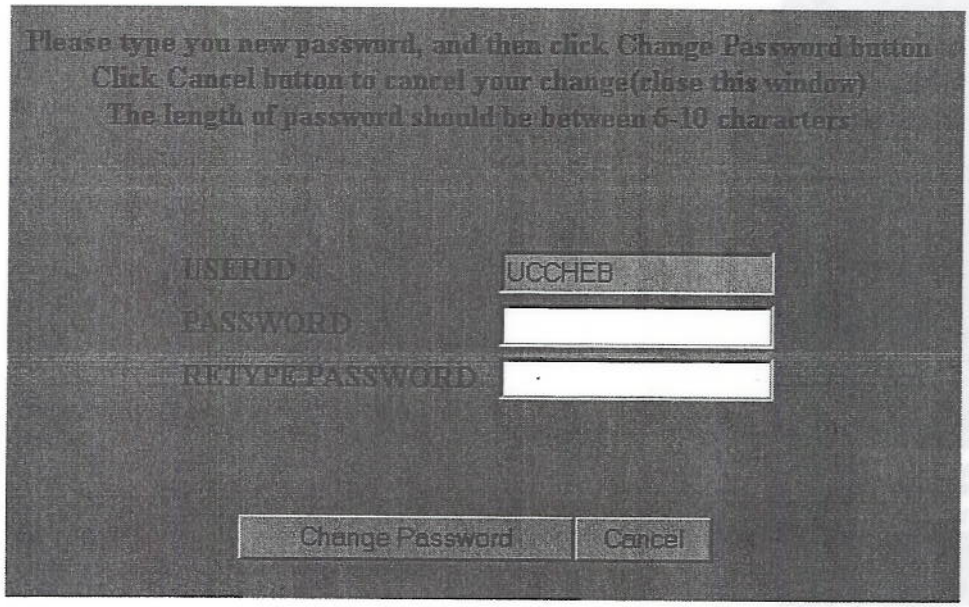
14.7 Utilities

The Utilities are a set of programs with perform functions outside normal data entry and reporting. To run the Utilities, choose Utilities from the CUTIE main menu. The Utilities menu is displayed:


RIVUR
Randomized Intervention for Children with Vesicoureteral Reflux
Select A Utility
Change Password
User Account Management

14.7.1 Change Password

Each user can change his own password by running the 'Change Password' utility. You are prompted to enter your new password and then re-enter it for confirmation:



If you enter a valid password and confirm it, you get the message:

14.7.2 User Account Management

The User Account Management utility is used to create new users, assign them privileges and change the privileges of existing users.

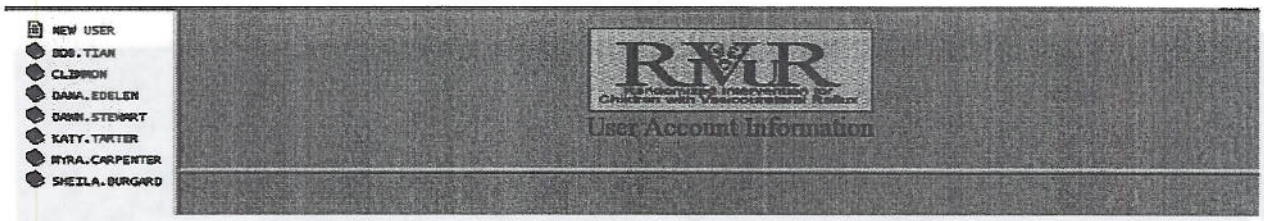
Privileges are granted or revoked for groups of tasks such as entering forms, running reports and running utilities. Each group of tasks has an associated set of permissions. The default groups are Form_alluser, Form_enrollment, Report_alluser, Utility_Coordinator and Utility_alluser. The default permission set for each group is as follows:

Task	Default Permission
Form_Alluser	Add, browse, change, delete
Form_Enrollment	Ability to enroll a patient
Report_Alluser	View all available reports
Report_Radiology	Report for radiologists
Utility_coordinator	Account management, change password, other study utilities such as data upload
Utility_alluser	Change Password

A user who has permission for Utility_coordinator can grant or revoke the default permissions for any task for any user using 'User Account Management'. For most users, Utility_alluser is the appropriate utility group. This allows them to change their own passwords but nothing else.

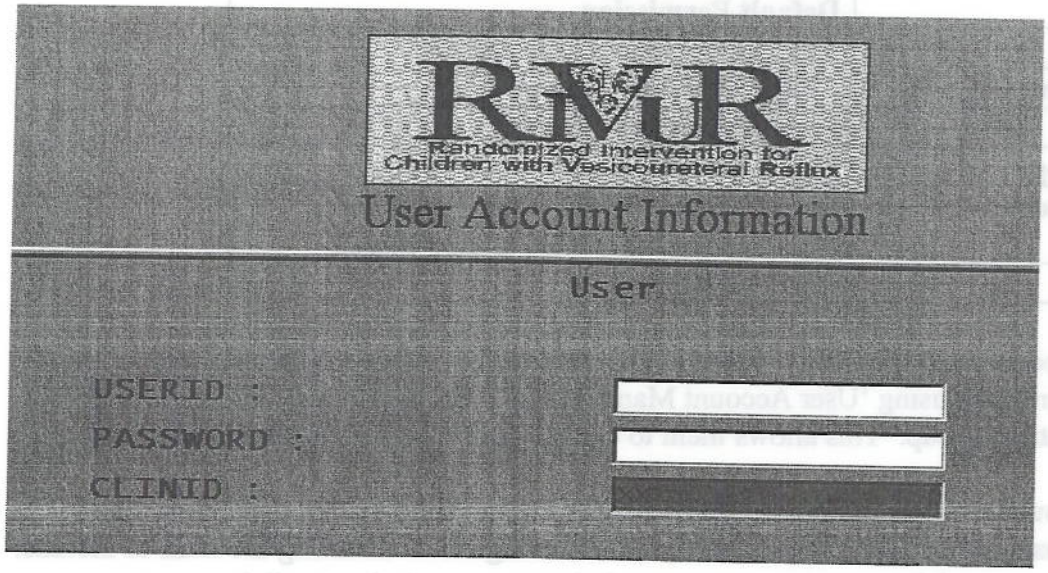
These are the groups and permissions set up by default. If, at your site, you need more finely tuned permissions, please make a request to the coordinating center detailing the tasks to include. For example, you may wish to grant some users only browse permission to all forms or you may wish to allow some users full access to a subset of forms

When you select User Account Management from the Utility menu the following screen is shown:



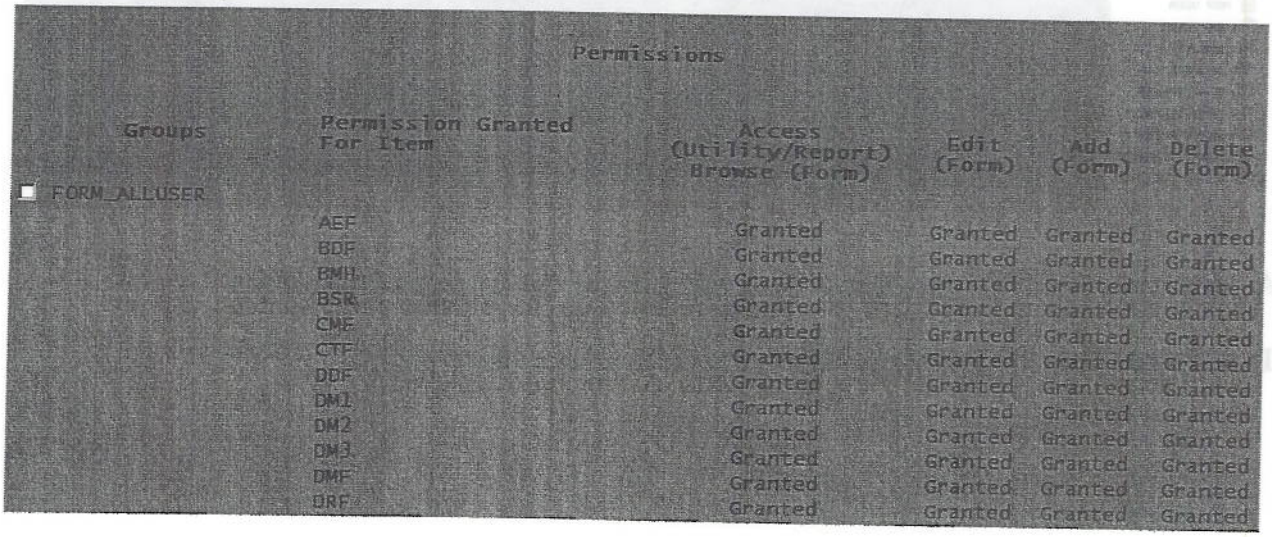
All user names from the current user's site are listed on the left side of the screen.

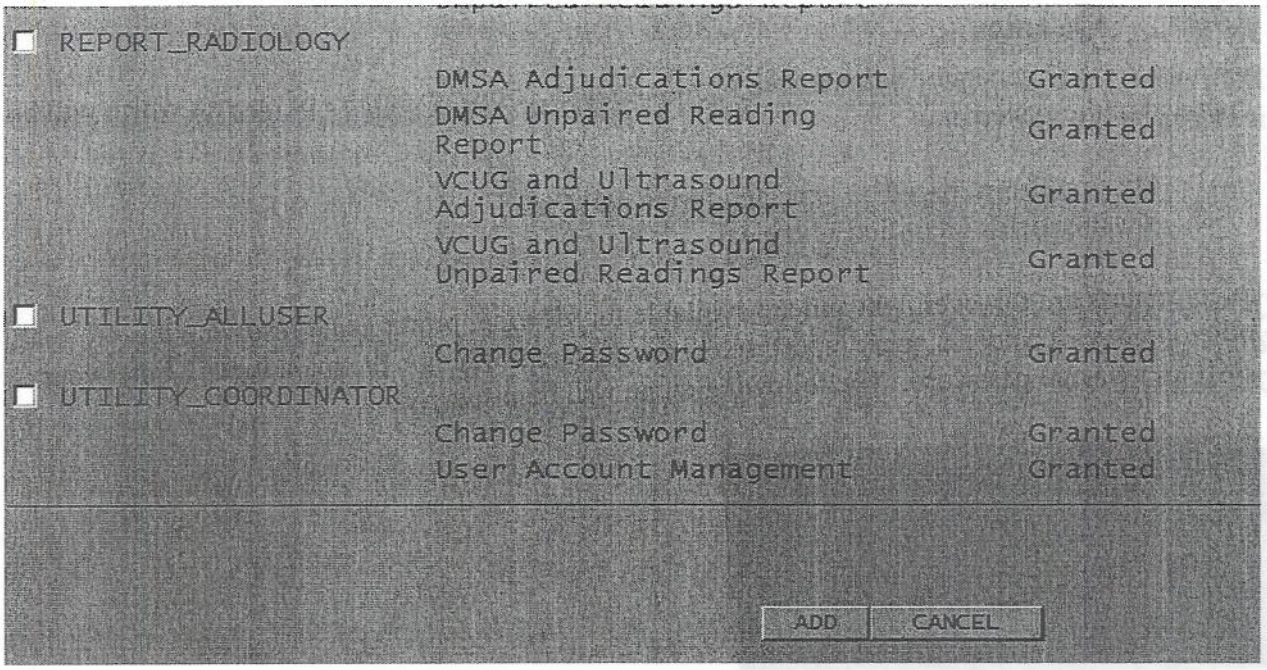
To add a new user, click the 'New User' item. A screen is displayed:



Enter the user name and password in the top panel.

Select the privileges to grant to the user in the second panel. Click the 'Add' button to add the user.





Click 'Add' to add the new user.

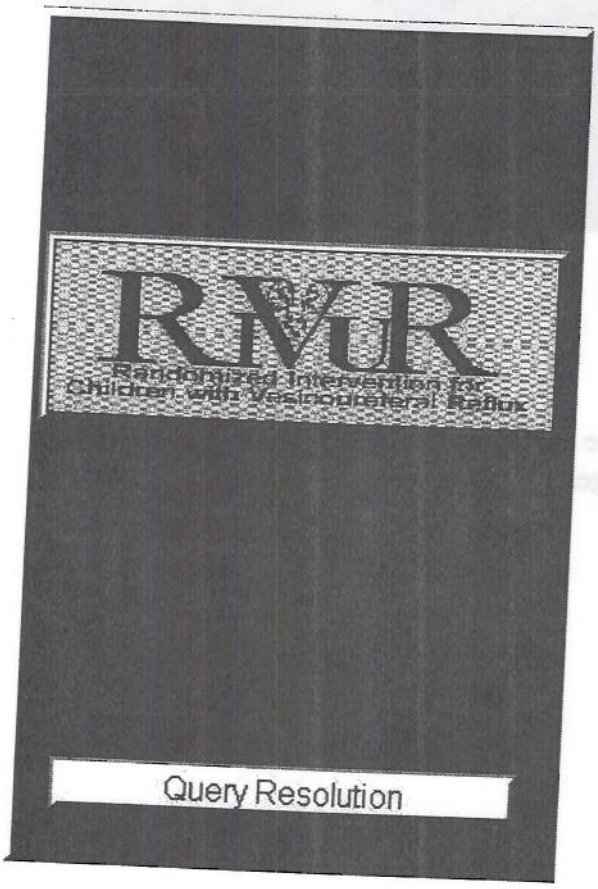
To change the password or privileges of a user, select the user from the list and make the desired changes. Click the 'Update' button to commit the changes.

14.8 Queries

Data queries are generated automatically by the system. Some examples of queries which will be included in the system are:

1. Missing forms, based on expected forms per visit.
2. Missing fields identified as critical.

Query reports are run overnight and are available for viewing, printing and resolving the following day. To access query report, select the "Queries" item on the main menu. Enter your DMS user ID and password. The following menu will be displayed:



Select 'Query Resolution' to go into a data entry system which allows you to resolve queries. The menus and features are almost identical to normal data entry. The main difference is that when you display a form which contains outstanding queries, only the fields involved in a query are accessible. The other fields are only for display.

14.9 DMS Updates

During the course of the study, the coordinating center will update the Data Management System software. These updates may include new or updated forms for data collection, new features or reports, and corrections for errors which are detected in the system. Each update will include a memorandum detailing the changes to the DMS which are included in the update. Please insert this memorandum at the end of the User's Guide so that it includes the most up-to-date information about the DMS.

Appendix 14.1 – CUTIE DMS Quick Start Instructions

These instructions are intended to serve as a quick reference for using the CUTIE Data Management System (DMS), and are not a substitute for mastering the contents of the User's Guide.

Whom do I contact if I have a problem / question / concern?

Contact Sheila Burgard or Myra Carpenter at the CUTIE Coordinating Center.

Starting the System

Connect to the CUTIE Web site at https://dms.cscc.unc.edu/RIVUR using Windows Internet Explorer 6.
Log in to Windows with your Windows ID and password.
Choose an option from the CUTIE DMS menu.
Log in to the DMS by keying your initials and your password. If you key the wrong initials, go ahead and key your password. You'll see the message "Login Failed." Key both in again.

Exiting the System

To exit the system, close IE6.

Appendix 14.2 – CUTIE Data Management System Security

Several measures are in place on the CUTIE Web server to ensure the security of study data. The site runs SSL (secure sockets layer) to encrypt data as it is transmitted from the user to the server. The SSL encryption is provided by 128 bit session keys provided by digital certificates. A user must provide a Windows 2000 user name and password to access the CUTIE main menu. To use the DMS, the user must also supply a DMS user name and password. Users have differing permissions. Users with full permission can add, change and delete records, enroll participants and run reports. Other users may only have permission to browse records and view reports.

The servers hosting the CUTIE DMS Web site have implemented many security measures recommended by security experts such as disabling unused ports and services, applying all operating system and Internet Server patches as they are released and running automated reports on certain access logs.