CHRONIC KIDNEY DISEASE IN CHILDREN PROSPECTIVE COHORT STUDY (CKiD) – STUDY PROTOCOL

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Table of Contents

CKiD STUDY PROTOCOL

1. INTRODUCTION

1.1 Overview

The Division of Kidney, Urologic, and Hematologic Diseases (DKUHD) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in collaboration with the National Institute of Child Health and Human Development (NICHD) and the National Heart, Lung and Blood Institute (NHLBI) funded a cooperative agreement including two Clinical Coordinating Centers, a Data Coordinating Center and Central Biochemistry Laboratory to conduct a prospective epidemiological study of children with chronic kidney disease (CKD). The primary goals of this study are to determine the risk factors for decline in kidney function and to define how a progressive decline in kidney function impacts neurocognitive function and behavior; the risk factors for cardiovascular disease; and growth failure and its associated morbidity.

1.2 Specific aims

The specific aims are to:

1. Identify novel and traditional renal disease risk factors for the progression of CKD (e.g. decline of GFR) in children,
2. Characterize the impact of a decline in kidney function on neurodevelopment, cognitive abilities, and behavior,
3. Identify the prevalence and evolution of traditional and novel cardiovascular disease risk factors in progressive CKD, and
4. Examine the effects of declining GFR on growth and the treatment of growth failure, and to assess the consequences of growth failure on morbidity in children with CKD.

1.3 Hypotheses

The study will address the following hypotheses:

1. Children with mild to moderate chronic kidney disease secondary to structural causes have slower rates of declining GFR compared to those with acquired glomerular disease.
2. Accelerated CKD progression will be associated with a positive family history of kidney disease, black race, Hispanic ethnicity, lower socioeconomic status, elevated systolic and diastolic blood pressure, high nocturnal blood pressure, anemia, periods of accelerated growth, hyperparathyroidism and hyperlipidemia.
3. When indicated, early surgical intervention as well as the prescription and adherence to therapy with angiotensin converting enzyme inhibitors, angiotensin receptor blockers and aldosterone inhibitors will slow CKD progression.
4. Systematic measurements of GFR, centrally measured “true” serum creatinine, centrally based serum Cystatin C and comprehensive clinical data will yield GFR estimating equations with better accuracy

and more precision than current formulas based on height and serum creatinine.

5. Declining GFR will be associated with measurable declines in neurocognitive function, behavior and quality of life in children with CKD. The greatest deficit in cognitive function will be seen in children with the longest duration of CKD, the highest stage of CKD and with the lowest hemoglobin levels.
6. Progressive CKD will adversely affect central nervous system conduction pathways, and detectable anatomic changes (white matter changes) will correlate with changes in neurocognitive status and GFR.
7. The prevalence and severity of traditional cardiovascular disease (CVD) risk factors (hypertension, hyperlipidemia) and uremia-related CVD risk factors (inflammation, malnutrition, anemia, hyperparathyroidism), will be associated with the progression of CKD.
8. The prevalence and severity of systemic and nocturnal hypertension will be associated with the decline of GFR and the development of concentric left ventricular hypertrophy (LVH). The prevalence and severity of anemia will be correlated with GFR decline and the development of eccentric LVH.
9. LVH will be responsible for decreased LV diastolic function in children with CKD.
10. Decreased aortic wall compliance will be related to elevated systolic blood pressure, hyperlipidemia, biomarkers of inflammation and increased Ca x P product.
11. Growth failure will be associated with the severity of secondary hyperparathyroidism, biomarkers of inflammation, poor nutrition, extent of GFR decline and early age at onset (i.e., prolonged duration of CKD).
12. Growth failure in children with CKD will be associated with a higher rate of morbidity, including increased hospitalizations, decreased quality of life, poor neurocognitive outcome and increased cardiovascular complications.
13. The response to recombinant human growth hormone (rhGH) treatment will be positively associated with GFR, serum bicarbonate level and nutritional status and negatively correlated with high sensitivity C reactive protein level, and severity of secondary hyperparathyroidism.

The proposed cohort study has been designed to measure variables in four scientific domains: kidney, neurocognition, cardiovascular and growth. The protocol was determined to optimize the power of the cohort design whereby levels and changes of exposure of interest temporally precede outcomes.

2. BACKGROUND

By 2020, it has been estimated that 785,000 Americans will have end stage renal disease (ESRD) at a cost of $28 billion per year. The increasing prevalence of chronic kidney disease (CKD) in the United States has motivated efforts to define potentially treatable risk factors for progression of CKD and its complications. Because the increase of CKD has been most dramatic in the adult population, few studies have been performed in children with CKD. However, because of the importance of growth and neurocognitive development in the pediatric age group, children are likely to be much more vulnerable to the effects of progressive CKD than adults. Additionally, as kidney disease is usually due to a primary urologic problem or glomerular disease rather than a secondary process such as diabetes or hypertension (HTN), as in adults, the risk factors and consequences of kidney disease progression, independent of other complicating factors, are likely to be clearer in children. These facts underscore the importance of investigating pediatric CKD with a prospective cohort study.

Although alarming increases in the rates of ESRD have occurred in older Americans, young adults with ESRD bear a significant percentage of the burden of disease. The 2001 United States Renal Data System (USRDS) Annual Data Report shows that 14% of incident hemodialysis (HD) patients, 22% of incident peritoneal dialysis (PD) patients and 42% of incident transplant patients are between 20 and 44 years of age. If the current estimate of 3-5 ml/min/year for the rate of decline in kidney function among adult patients with CKD is correct [Hunsicker 1997, NAPRTCS 2002, Wright, Jr. 2002], then many young adults with end stage kidney disease had the genesis of their CKD in childhood or adolescence.

Most children with CKD have congenital urologic disease or inherited disorders. The most common causes of pediatric CKD are: obstructive uropathy, renal dysplasia, reflux nephropathy and focal segmental glomerulosclerosis [NAPRTCS 2002]. Unlike adults who have completed their physiological and intellectual maturation, infants and children are at the early stages of their developmental processes and are particularly vulnerable to the adverse effects of chronic disease. The metabolic alterations associated with kidney failure are known to be associated with abnormal growth, delayed pubertal development, decreased red blood cell production, deregulation of bone homeostasis, increased risk of cardiovascular disease and impaired neurocognitive function. Although there is a fundamental understanding of the problems that occur at severe stages of renal insufficiency, relatively little is known about the effects of early stages of CKD on the evolution of these abnormalities in children.

To date there have been few large-scale prospective studies of children with CKD. By collecting longitudinal data on a cohort of approximately 600 children and adolescents with CKD, we will have the opportunity to understand the heterogeneity in the decline of renal function in children. By using standardized criteria and concurrently collecting data on neurocognitive development, markers of cardiovascular risk, growth failure and its sequellae, this study will provide the necessary information to establish the sequence of associations between renal disease progression, the development of neurocognitive and cardiovascular co-morbidity, and growth failure.

2.1 Progression of Chronic Kidney Disease

To slow the progression of CKD, and treat the complications of CKD during the formative years of life, an in-depth understanding of the risk factors for progression of pediatric CKD is necessary. Information from the North American Pediatric Renal Transplant Cooperative Study [NAPRTCS 2002] Chronic Renal Insufficiency (CRI) registry, with data on over 5000 children with CKD, suggests several risk factors for renal progression in children [NAPRTCS 2002]. Important risk factors identified by this registry include age (preteen and teenage children progress to ESRD more rapidly than younger children), underlying disease (focal segmental glomerulosclerosis vs. other disorders), and low GFR at entry into the registry. Hypertension, proteinuria, poor nutrition, anemia, hypocalcemia, hyperphosphatemia and hyperparathyroidism are also associated with rapid progression to ESRD.

In adults, race [Brancati 1992, Feldman 1992, Klag 1997, Whittle 1993], family history [Freedman 1993], diet, physical activity, smoking, socioeconomic status, and medical management are associated with progression of CKD, while proteinuria [Iseki 1997, Klahr 1988, Levey 1991, Lewis 1993, Maschio 1996, Ruggenenti 1999], hyperlipidemia, and inflammation [Kasiske 1998, Ruggenenti 2000, Sarnak 2000] are intermediate factors affecting progression. Therefore, risks due to host factors (e.g., genetic susceptibility, sex, race, serum albumin <4 g/dl, phosphate >5.5, proteinuria, hypertension, anemia, and others), exposures external to the host, and medical management will be systematically studied in this prospective cohort of children with CKD. Not only will this study examine traditional risk factors for kidney disease progression, we will attempt to identify novel markers for kidney disease progression. Prospective, standardized data collection and precise measurements of GFR will allow more precise definition of risk factors and will allow us to differentiate between causal and non-causal associations. Non-causal associated factors can be markers for other causal factors (confounding) or markers of the disease itself (reverse causality).

2.2 Neurocognitive Development in Children with CKD

Historically, CKD in infancy was thought to cause high rates of retardation, microcephaly and seizures [Rotundo 1982], but such gross developmental delays are now less common [Warady 1999, Warady 2002], likely due to aggressive treatment of malnutrition and avoidance of aluminum-containing compounds. However, there is virtually no comprehensive and prospective information on the neurocognitive impact of a decrease in renal function that develops later in childhood. Many small cross-sectional studies [Crocker 2002, Fennell 1990a, Fennell 1990b, Hulstijn-Dirkmaat 1995, NAPRTCS 2002, Polinsky 1987] suggest that children with CKD are at risk for delays in neurocognitive development but the prevalence, incidence, and magnitude of developmental delays remain largely unknown.

Previous studies suggest specific cognitive and neuro-developmental deficits occur with ESRD, especially when it occurs in infants. Global developmental delay, delay in gross motor skills, overt hypotonia, and impaired language development have been reported in 20-65% of young infants and toddlers with ESRD [Polinsky 1987,Warady 1999]. Older children with ESRD show specific deficits in intelligence quotient (IQ),

achievement, memory, visual spatial skills, attention and executive cognitive functions [Brouhard 2000, Fennell 1986, Fennell 1990b, Mendley 1999].

Many factors may influence the severity of cognitive deficits in children with CKD especially age of onset [Crittenden 1985, Rasbury 1986] and duration of kidney failure [Fennell, III 1984, Rasbury 1983]. Other factors, related both to kidney failure and to cognitive function may confound the association between progressive CKD and developmental dysfunction. These potential confounding factors include: anemia, recognized to be associated with delayed development in children and impaired cognitive function in adults [Halterman 2001, Lawry 1994, Marsh 1991, Sagales 1993], and depression which adversely affects attention span and memory and clearly affects both children and adults with ESRD. Careful measurement of these factors must be included in any evaluation of neurological impairment in children with CKD. This study will obtain baseline measurements of cognitive function within 6 months of the baseline GFR assessment, depending on the age of the child. In addition, this study will obtain subsequent biannual (at odd years) neuropsychological, behavioral, and psychiatric assessments on all subjects in this cohort. Quality of life will be assessed annually. To explore whether changes in GFR are associated with subsequent anatomic and structural changes in the brain, a subset of patients had further testing with Magnetic Resonance Imaging (MRI). The CKiD study is the first large-scale attempt at systematically studying the impact of renal disease on neurocognitive function in children. This study will yield much needed information on the impact of renal disease on neurocognitive function and will serve to characterize the impact of chronic kidney disease on quality of life.

2.3 Cardiovascular Disease in Children with CKD

Cardiovascular disease (CVD) is a major problem in adults with kidney dysfunction, but the incidence and types of CVD present in children with CKD is unknown. The cardiovascular mortality rate reported in children and young adults on chronic dialysis is almost 1000 times higher than in the general population at comparable ages [Parekh 2002]. According to the USRDS 2000 [USRDS 2002] report, 33% of all deaths in children with ESRD were related to cardiovascular causes. In NAPRTCS, 38-78% of children are hypertensive [Fivush 1998, Mitsnefes 2003a] and as many as 60-90% develop hyperlipidemia [Querfeld 1993] and hyperhomocysteinemia [Kang 2002, Lilien 1999, Merouani 2001]. However, it is not clear how these cardiovascular risk factors impact changes in cardiac geometry and function as kidney disease progresses.

Echocardiographic studies in patients with CKD demonstrate identifiable and measurable cardiovascular changes that are associated with renal disease. These include geometric changes which manifest themselves as: left ventricular hypertrophy and increased left atrial size; functional changes in systole and diastole; and vascular changes. Echocardiographic studies of children in all phases of treatment for kidney insufficiency have revealed an increased left ventricular mass (LVM) in 22% of the children with CKD, 30% in those treated with dialysis and in 63% of the transplant group [Johnstone 1996]. An important association has also been noted between LVM and decreasing kidney function in patients with CKD. The clinical sites in the current study

have the capabilities to obtain serial echocardiographic measurements in a standardized fashion by trained technicians using conventional M-mode and 2-D equipment. All participants in this study will undergo baseline echocardiographic assessment to be measured at the second visit with a concurrent GFR, as well as follow up echocardiographic assessments to monitor cardiac function.

This study will systematically assess host risk factors (e.g., genetic susceptibility, age, sex, race, hypertension, malnutrition, lipid abnormalities, proteinuria, inflammation, and anemia) and medical management that may be associated with cardiac dysfunction and echocardiographic changes.

Hypertensive target-organ damage (TOD), including left ventricular hypertrophy (LVH) and increased carotid and aortic stiffness, occur commonly in adults with CKD, and they have independent, deleterious effects on survival, particularly after the initiation of dialysis [Blacher 1999, Chavers 2002, Paoletti 2002, Stack 2002]. Although some forms of hypertensive TOD, most notably LVH, may be seen in children with CKD at the initiation of dialysis [Mitsnefes 2001], the prevalence of hypertensive TOD in children with less advanced CKD is unknown. Abnormalities of 24-hour BP profile in hypertensive children studied by ambulatory blood pressure monitoring (ABPM) are clearly associated with TOD, including decreased creatinine clearance, increased carotid intima thickness, and LVH. Harsfield et al reported that black adolescents had higher BP during sleep than whites, which was associated with decreased creatinine clearance [Harshfield 1994]. Doppler imaging of the ascending and abdominal aorta can be used to determine aortic stiffness, which has an independent effect on patient survival in adults with CKD [Blacher 1999]. Although such changes have not yet been described in children with CKD, carotid changes have been demonstrated in hypertensive children [Sorof 2003], suggesting that vascular damage, like LVH, is a likely finding in this population. This study will collect blood pressure data by clinic blood pressure measurement and 24-hour ABPM. This will be important to assess the effect of BP measures and its effect on cardiovascular status and renal progression.

With these assessments in place, this cohort study will determine the prevalence, incidence and the magnitude of CVD and assess both novel and traditional risk factors for CVD in children with CKD. CKiD will have the potential to guide recommendations and research for the prevention and/or treatment of these abnormalities as CKD progresses.

2.4 Growth Failure and Bone Disease in Children with CKD

Growth failure is highly prevalent in children with CKD, and is a significant cause of morbidity and mortality. Utilizing the United States Renal Data System's [USRDS 2002] Pediatric Growth and Development Special Study, Wong et al demonstrated that poor incremental growth was associated with an increased risk of death in children with ESRD [Wong 2000]. Furthermore, children with growth failure had an increased risk of morbidity with a 14-25% increased risk of hospitalization compared to patients with normal growth [Furth 2000]. Analysis of 1,988 children <21 years of age enrolled in the dialysis component of NAPRTCS, has shown similar results [Furth 2002a, Furth 2002b].

Those children with a standardized height deviation score of <-2.5 had a two-fold higher risk of death compared to those initiating dialysis with a height standard deviation score of >-2.5. The more severely growth retarded patients also had more hospital days per month of dialysis and were less likely to attend full-time school. Growth retardation is a risk factor for increased morbidity and mortality in children with CKD. However, it is not clear whether growth failure is a cause of worse outcomes in CKD or a marker for more severe disease, poor care or non-compliance. Therefore, it is important to further delineate whether optimal management of growth retardation can reduce the burden and cost of hospitalization and mortality in these patients.

Multiple factors contribute to CKD-related growth retardation, such as age at initiation of CKD, type of primary renal disease, concomitant acidosis, malnutrition from calorie deprivation, anemia and secondary hyperparathyroidism, with or without accompanying renal osteodystrophy. A seminal finding was the discovery that perturbations of the growth hormone insulin like growth factor (GH/IGF) axis are prevalent in CKD and a predominant factor for the impaired growth associated with CKD [Tonshoff 1990]. Observations that recombinant growth hormone (rhGH) treatment improved the growth velocity of children with CKD has dramatically changed the therapeutic approach to the growth retardation of CKD [Koch 1989]. Since a positive change in standardized height (i.e., catch up growth) is unlikely to occur under dialysis despite the use of rhGH and typically only occurs in the youngest (<6 years) transplant recipients, the potential achievement of a normal adult height in patients with impaired kidney function mandates aggressive attention to this issue during the period of CKD and the use of rhGH has been particularly beneficial to this end [Koch 1989].

A variety of studies have shown that the majority of pediatric patients with CKD exhibit an inadequate dietary energy intake [Holliday 1972, Kuizon 1999, Norman 2000, Ratsch 1992, Salusky 1983], which progressively worsens with decreasing renal function [Betts 1974]. Since energy intake is the principle determinate of growth during infancy, it suggests that malnutrition may have the most marked negative effect on growth in children with congenital disorders leading to CKD [Betts 1977].

Bone disease is a universal complication of chronic kidney disease, and it encompasses a spectrum of skeletal disorders which include the high-turnover lesions of secondary hyperparathyroidism and the low-turnover lesion of adynamic renal osteodystrophy [Goodman 1999]. To date, serum biochemical determinations have been poor predictors of bone histology in pediatric patients undergoing dialysis, as well as in those with chronic kidney failure [Hodson 1982, Hsu 1982, Norman 1980, Salusky 1988, Witmer 1976]. Based upon the study of a small number of patients, target parathyroid (PTH) levels have been suggested for the diagnosis of renal osteodystrophy in pediatric patients with CKD and for those in dialysis [Mathias 1993, Salusky 1994, Sherrard 1993].

Salusky, et al. [Salusky 1998] determined the relationship between PTH levels measured by 1st PTH-IMA and bone formation rate in 20 children aged 8±5 years, with chronic renal insufficiency, not yet on dialysis (calculated GFR: 36±22 ml/min/1.73m^2).

The children underwent iliac crest bone biopsy after double tetracycline labeling [Goodman 1994, Salusky 1998, Salusky 1988, Salusky 1994]. At bone biopsy, none of the patients were receiving active vitamin D sterols and half of the patients were receiving calcium-containing phosphate binders. Mean serum calcium and phosphorus concentrations were 9±0.2 and 5±1.2 mg/dl respectively. For the entire group, the mean serum PTH concentration was 114±111 pg/ml; in patients with normal bone formation rates, serum PTH levels were 65±32 pg/ml and in those with histologic evidence of secondary hyperparathyroidism, PTH levels were 222±157 pg/ml. Of note, in pediatric patients treated with dialysis, the latter values were associated with adynamic osteodystrophy rather than high-turnover lesions [Salusky 1988, Salusky 1994]. For the entire group, PTH values and bone formation rates were highly correlated, $r=0.78$, $p<0.01$. Although the sample size was small, these preliminary observations provide the stimulus for the need to define the levels of PTH that are associated with normal rates of bone formation in patients with different degrees of kidney insufficiency.

Finally, over the last two decades, the use of therapy with active vitamin D metabolites, the most common being Calcitriol, has been recommended for children with kidney failure in order to prevent secondary hyperparathyroidism and improve growth velocity [Chesney 1978]. However, secondary hyperparathyroidism remains the predominant lesion of renal osteodystrophy in children treated with dialysis despite daily therapy with Calcitriol. Of interest, severe growth retardation has been observed in children receiving peritoneal dialysis when treatment with intermittent Calcitriol has been introduced and results in low bone turnover [Kuizon 1998]. Thus, both control of secondary hyperparathyroidism and prevention of adynamic bone are needed in order to maximize growth velocity.

Furthermore, current evidence indicates that hypercalcemia, hyperphosphatemia, and use of active Vitamin D sterols may be implicated in the process of vascular calcifications that have been seen in young adults that initiated dialysis therapy in childhood [Goodman 2000, Oh 2002]. These seminal findings suggest that disturbances unique to CKD and separate from traditional cardiovascular risks may contribute to the high incidence of coronary artery calcifications, and possibly CVD in those patients with CKD.

3. STUDY ORGANIZATION

3.1 Overview

The CKiD is a cooperative agreement between two clinical coordinating centers, a data coordinating center, a central biochemistry laboratory and the NIDDK Division of Kidney, Urologic and Hematologic Diseases. Additional funding is provided by the National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute. The CKiD maintains central laboratories and repositories for biological specimens and genetic material. The CKiD is directed by a steering committee, which decides upon study policies.

3.2 Clinical Coordinating Centers

The mid-west clinical coordinating center is directed by Dr. Bradley Warady (Principal Investigator [PI]) at the Children's Mercy Hospital in Kansas City, MO. The east-coast clinical coordinating center is directed by Dr. Susan Furth (PI) at Children's Hospital of Philadelphia in Philadelphia, PA (previously at the Johns Hopkins Medical Institutions in Baltimore, MD). Each clinical coordinating center has identified a consortium of clinical sites, at which children will be recruited and followed up.

3.2.1 Clinical Sites

The approximately 50 CKiD study sites are geographically shown in Figure 3.2.1 and listed in Tables 3.2.1 and 3.2.2.

Figure 3.2.1

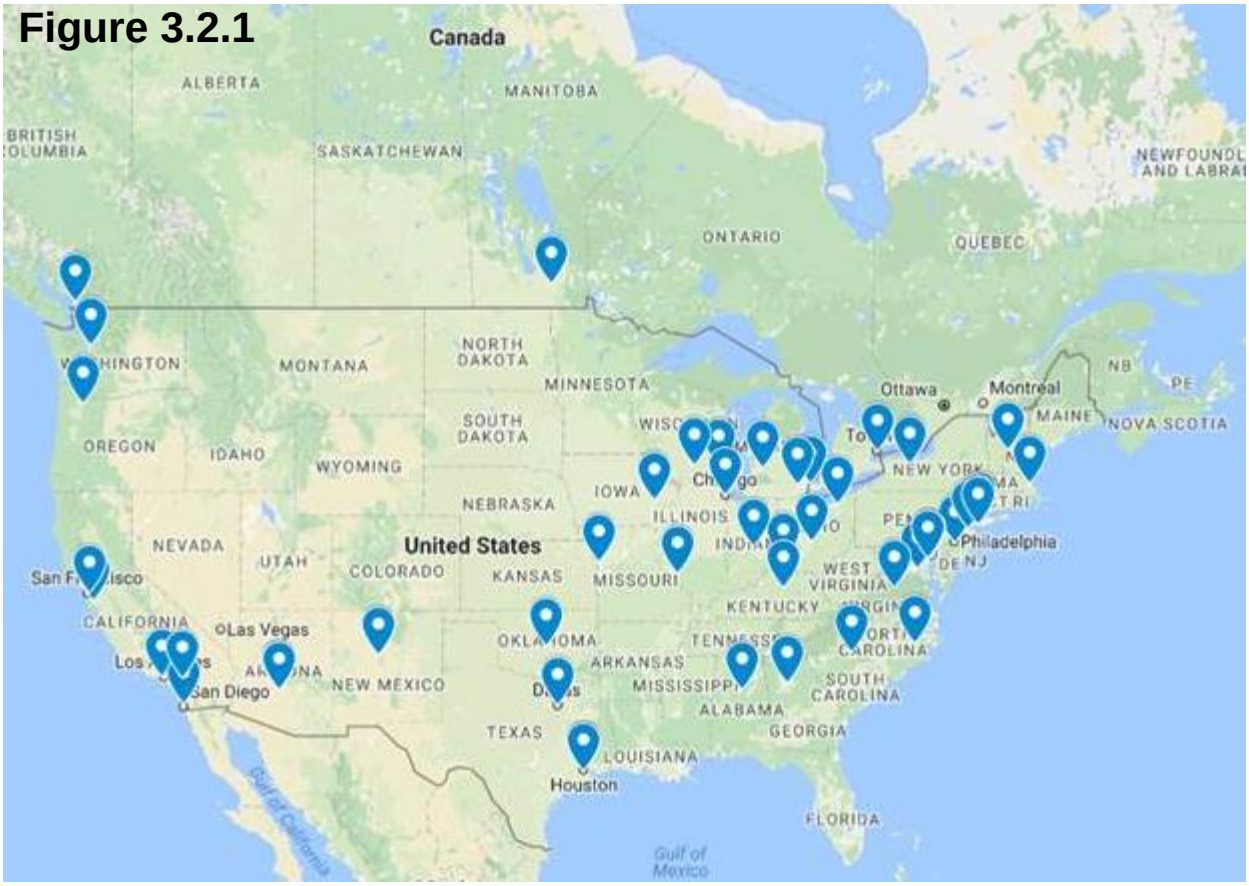


Table 3.2.1

CHILDREN'S MERCY HOSPITAL SITES		
#	**Name**	**PRINCIPAL INVESTIGATORS**
33	Arizona Kidney Disease and Hypertension Center	Gina Marie Barletta, MD*
8	British Columbia Children's Hospital	Tom Blydt-Hansen, MD, FRCPC *
28	Egleston Children's Hospital, Emory University	Larry Greenbaum, MD, PhD*
5	Cincinnati Children's Hospital Medical Center	Donna Claes, MD*; Mark Mitsnefes, MD
15	Seattle Children's Hospital	Joseph Flynn, MD*
9	Children's Hospital of Alabama	Sahar Fathallah, MD
7	Boston Children's Hospital	Nancy Rodig, MD*; William Harmon, MD
17	Children's Hospital of Winnipeg	Allison Dart, MD MSc, FRCPC *
1	Children's Mercy Kansas City	Bradley Warady, MD*
2	Medical College of Wisconsin	Cynthia Pan, MD*
13	University of Oklahoma Health Sciences Center	Anjali Nayak, MD*
4	Oregon Health and Science University	Amira Al-Uzri, MD*; Randall Jenkins, MD
27	Phoenix Children's Hospital	Martin Turman, MD, PhD*
11	Case Western Reserve University	Katherine Dell, MD*
10	St. Louis Children's Hospital	Keefe Davis, MD*
6	Stanford University Medical Center	Cynthia Wong, MD*; Steve Alexander, MD
25	UCSF Children's Hospital	Elaine Ku, MD, MAS*
20	University of California – Los Angeles	Isidro Salusky, MD; Ora Yadin, MD*
21	University of California – San Diego	Nadine Benador, MD*; Robert Mak, MD, PhD
3	University of New Mexico Children's Hospital	Craig Wong, MD, MPH*
22	University of Texas Southwestern Medical Center	Mouin Seikaly, MD*
12	University of Wisconsin	Sharon Bartosh, MD*

* Clinical Site Principal Investigator

Table 3.2.2

CHILDREN'S HOSPITAL OF PHILADELPHIA SITES		
#	**Name**	**PRINCIPAL INVESTIGATORS**
52	Ann & Robert H. Lurie Children's Hospital of Chicago	Craig Langman, MD*
80	Carolinas Medical Center	Susan Massengill, MD*
83	Children's Hospital of Philadelphia	Susan Furth, MD, PhD*
51	Children's Hospital of Michigan	Tej Matoo, MD*
86	Children's Hospital at Dartmouth	Adam Weinstein, MD*
64	Children's Hospital at Montefiore	Frederick Kaskel, MD, PhD*
53	Children's National Medical Center	Larry Patterson, MD*
79	DeVos Children's Hospital at Spectrum	Alejandro Quiroga, MD*
85	East Carolina University	Guillermo Hidalgo, MD*
84	Hospital for Sick Children (Sick Kids)	Rulan Parekh, MD*; Lisa Robinson, MD
55	INOVA Fairfax Hospital for Children	Patricia Seo-Mayer, MD*
50	Johns Hopkins Children's Center	Meredith Atkinson, MD*
57	Indiana University, Riley Hospital for Children	Amy Wilson, MD*
68	Icahn School of Medicine at Mount Sinai	Jeffrey Saland, MD*
89	Loma Linda University	Cheryl Sanchez-Kazi, MD*
54	Nationwide Children's Hospital, Ohio State University	Amy Kogon, MD*
74	RBHS-Robert Wood Johnson Medical School	Joann Carlson, MD*
81	State University of New York, Downstate Medical Center	Anil Mongia, MD*
70	Texas Children's Hospital	Poyyapakkam Srivaths, MD
82	University of Illinois at Chicago	Eunice John, MD*
65	University of Iowa	Jason Misurac, MD*
88	University of Kentucky	Stefan Kiessling, MD*
58	University of Maryland	Susan Mendley, MD*
59	University of Michigan, Mott Hospital	Dave Selewski, MD*
72	University of Rochester Medical Center, Golisano Children's Hospital at Strong	Marc Lande, MD*; George Schwartz, MD
61	University of Texas, Houston	Joshua Samuels, MD*
73	University of Virginia	Victoria Norwood, MD*

* Clinical Site Principal Investigator

3.3 Data Coordinating Center

The DCC, KIDMAC (Kidney Disease in children Data Management and Analysis Center) is part of the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health. The Principal Investigator is Dr. Alvaro Muñoz. KIDMAC will be responsible for the data analysis, data management and overall study coordination.

3.4 Central Laboratories

KIDMAC has linked with the laboratory of Dr. George Schwartz at the University of Rochester School of Medicine and Dentistry in Rochester, NY, to establish the central laboratory for measuring the primary outcomes of the study. Specifically, Dr. Schwartz's laboratory will measure GFR based on clearance of Ioxehol, serum creatinine, cystatin C, uric acid, urine creatinine, urine protein, urine albumin, central renal panel, lipid profile, intact parathyroid hormone, high sensitivity C reactive protein and vitamin D. Laboratory results will be available on NEPHRON, the data management system for the

CKiD study. NEPHRON is located at https://statepiaps6.jhsph.edu/nephron/groups/aspproc/. For Cohort 1, investigators affiliated with the mid-west CCC played the role of the central laboratory for measuring cystatin C at baseline (Children's Mercy Hospital); however, for Cohorts 2 and 3, cystatin C will be measured at the CBL. Mid-west affiliates play the role of the central reading centers for echocardiograms, carotid intima-media thickness and cardiac magnetic resonance imaging (MRI) (Cincinnati Children's Hospital). Investigators affiliated with the east-coast CCC will coordinate the calibration of instruments for ambulatory blood pressure measurements, and interpretation of these results (University of Texas-Houston Medical School) and standardized methods for clinical blood pressure measurements (Seattle's Childrens Hospital). In addition, University of North Carolina (affiliated with the east coast CCC) was the central laboratory for the brain MRI that was done in a small subset of the cohort. The University of North Carolina also coordinated central reading of the neurocognitive tests.

3.5 Central Repositories

The purpose of the CKiD repositories is to make samples available for ancillary studies and for future use in research of CKD in children after CKiD is complete. Participants will be given the option to contribute samples beginning at study visit 1b. Biological specimens will be sent to the biosample repository and whole blood will be sent to the genetic repository. Data will also be sent from the DCC to the data repository.

The NIH established contracts for the three repository sites and covers the expense of storage of deposited materials. Before samples are sent to the repositories, they will be labeled with the participant's study ID number and no other distinct personal identifiers such as name, social security number or medical record number. All repository specimens and data will be stored for the foreseeable future and without any personal identifiers. Participants will not receive any direct benefit or payment for the use of their specimens from the repository. Participants will be given the option to withdraw their samples stored in the repository up until the end of this study.

3.5.1 Repository for Biological Specimens

Biological Specimens will be stored at the NIDDK Biosample Repository, which is Fisher BioServices Corporation in Rockville, MD. Blood and urine specimens will be collected at the baseline visit and at each annual follow-up visit. Nail clippings and hair samples will be collected at baseline. Toe nail clippings will be collected at Visit 4.

3.5.2 Repository for Genetic Material

The genetics repository is the Rutgers, the State University of New Jersey in New Brunswick, NJ. The genetics repository will receive blood samples and process them to create immortalized cell lines, and DNA samples. The DNA samples may be shared with ancillary study investigators and possibly used for genome wide association studies (GWAS). Whole blood for the genetic repository will be collected at baseline.

3.5.3 Repository for Data

The NIDDK data repository is the Information Management Services (IMS). The data repository will receive, archive, and be able to distribute the CKiD public data.

3.6 National Public Databases

To further assist with understanding the progression of CKD, the study may obtain information about health status (e.g., dialysis, transplantation, vital status) from public health databases supported by government entities, such as the United States Renal Data System (USRDS), the Scientific Registry of Transplant Recipients (SRTR), the National Death Index (NDI), the Canadian Organ Replacement Register (CORR), the Canadian Institute of Health Information, etc. The goal of linking CKiD to US and Canadian databases is to capture primary outcome data about ESRD (dialysis, transplant) and death, including but not limited to, medication use, hospitalizations, lab test results and physical exam measurements among participants in the CKiD Study who provide consent to have their personal information used for this purpose. Additionally, as CKiD is a prospective longitudinal cohort study, it is expected that in-study observation or indirect data collection methods will not always be possible (whether due to lost-follow-up or the study ending at some point in the future). Such linkage will have the potential to add value of very long-term follow-up to the CKiD study through external data obtained outside of the study. In the US, national databases collect and file information by social security number, name, date of birth and gender. Canadian entities use the provincial health identification number, instead of SSN. Participants will be given the option to grant permission to the study to use their SSN, name, DOB and gender to periodically check if their health information is available in public health databases. Participants will not receive any direct benefit or payment for the use of their health information. As the aim is long-term follow-up of participants, linkage will occur every 5 to 10 years. We will also seek to conduct an initial “test” linkage to assess how the data merges with the known data obtained by CKiD about ESRD patients and to gain experience about the linking process so as to maximize the success of future linkages.

In addition to linking data of CKiD participants with national databases (i.e., matched individuals), the study will also obtain data of unmatched individuals. Unmatched individuals are patients whose medical information is already in the public health database but were never enrolled in the CKiD study. The data on unmatched individuals will not have personal identifiers i.e. name, address, SSN or medical record number, but will have similar information about individuals’ ESRD status such as dates of transplant, dates of dialysis, vital status, medication use, hospitalizations, etc. This data will augment the CKiD study in several ways. Principally, ESRD patients who were not CKiD participants may serve as a comparison group. Characterizing differences between CKiD participants who eventually developed ESRD and the broader population of contemporary patients who develop ESRD at similar ages will inform the generalizability of within-study CKiD findings.

3.6.1 Storing Personal Information

The public health databases will only be provided a generic identification number in conjunction with the participant's SSN, name, date of birth and gender.

3.6.2 Honest Broker

This study is designed to ensure that the Clinical Coordinating Centers and Data Coordinating Center do not receive personal identifiers except dates of birth. To maintain patient confidentiality, an Honest Broker will be used to prevent having medical/study data in the same place as personal identifiers. The Department of Biomedical and Health Informatics (DBHi) will serve as the Honest Broker. Although DBHi resides in the Children's Hospital of Philadelphia (CHOP), it is a separate and independent entity from the research team at the East Coast Clinical Coordinating Center located in the Nephrology Division at CHOP. The participant's CKiD study identification number, SSN, name, date of birth and gender will be provided directly from the participant's clinical site to the "Honest Broker". As the Honest Broker, DBHi will be the entity to provide the participant's personal identifiers (i.e., SSN, name, date of birth and gender) to the national databases. DBHi will create a generic identification number (DBHi ID) for each participant to safeguard the transmission of the CKiD study identification number with the national database. At the designated time of linkage, only the DBHi ID and participant's personal identifiers will be sent to the national database. The national database will merge the DBHi ID with the data from their national database and transmit the data back to the DBHi without the participant's personal identifiers. For unmatched individuals who are not participants in the CKiD study and do not have a DBHi ID, the national database will assign an encrypted identification number and transmit data to the DBHi without personal identifiers. Therefore, the data on unmatched individuals will not be identifiable to the Honest Broker. Upon receipt of data from the national database, the DBHi will remove the DBHi ID from matched individuals and replace it with the participant's CKiD study identification number prior to transmitting it to the DCC. Using this process, the DBHi will be the only entity with the participant's CKiD study identification number, DBHi ID and personal identifiers. Therefore, the final data set received by the DCC will have been de-identified by the DBHi. All data will be transmitted via encrypted password-protected files.

3.7 Committees

The CKiD is directed by a steering committee, which determines the need for, and scope of, permanent and temporary subcommittees. Subcommittees report to the steering committee. In addition to the steering committee, the NIDDK has established an observational study monitoring board (formally referred to as an external advisory committee) for this study.

3.7.1 Steering Committee

The CKiD Steering Committee (SC) is charged with the direction of the study. The SC consists of four voting members, the principal investigators for each of the two clinical coordinating centers, the principal investigator for the data coordinating center, and a representative from the NIDDK Division of Kidney, Urologic and Hematologic diseases. These voting members are Susan Furth, Bradley Warady, Alvaro Muñoz, and Ziya

Kirkali, respectively. Non-voting members of the SC are determined by the voting members. The non-voting members are: Alison Abraham, Kristin Burns, Judith Jerry-Fluker, Joseph Flynn, Arlene Gerson, Larry Greenbaum, Stephen Hooper, Rebecca Johnson, Frederick Kaskel, Paula Maier, Robert Mak, Mark Mitsnefes, Malot Minnick-Belarmino, Jacqueline Ndirangu, Derek Ng, Jeffrey Saland, Joshua Samuels, George Schwartz, Sarah Smiley, Christine Smith, Maleka Smith, Julia Starr, Perdita Taylor-Zapata and Craig Wong.

3.7.2 Observational Study Monitoring Board

The Observational Study Monitoring Board (OSMB) is 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. All recommendations of the OSMB will be considered by the SC. As the study is being conducted, annual meetings with the SC will be used to share the status of the study, new initiatives, findings, and publications. Members of the OSMB were selected due to expertise in specific areas of the protocol. The members of the OSMB are F. Bruder Stapleton (Chairperson), Aviva Goldberg, Blanche Chavers, Mark Schluchter, Avital Cnaan, Jami Levine, and Jeffrey R. Botkin.

3.7.3 Subcommittees Related to Specific Aims of CKiD

To facilitate the development of the study protocol, the SC formed four subcommittees structured around the four main scientific areas of CKiD: kidney disease progression, neurocognitive outcomes, cardiovascular outcomes, and growth outcomes. The charge of each scientific area-based subcommittee is to advise the SC on the scientific direction of CKiD. Each subcommittee is further charged with assisting in the development and ongoing revision of the data collection forms, the study protocol, and the Manual of Procedures related to the subcommittees' particular area. Finally, each subcommittee will advise the SC on the merit of submitted CKiD concept sheets, as needed (see section 3.8.2.1). Specific tasks of each subcommittee are listed below and a list of subcommittee members is shown in Appendix A.

3.7.3.1 Kidney Disease Progression Subcommittee

The Kidney Disease Progression Subcommittee is charged with identifying key risk factors and measurements in kidney disease progression; recommending procedures for measuring Glomerular Filtration Rate (GFR) and risk factors for progression of kidney disease; and establishing realistic costs of proposed measurements and procedures.

3.7.3.2 Neurocognitive Outcomes Subcommittee

The Neurocognitive Outcomes Subcommittee is charged with identifying key risk factors and measurements for neurocognitive function; recommending procedures for measuring relevant neurocognitive variables and neuroimaging studies; and establishing realistic costs of proposed measurements and procedures.

3.7.3.3 Cardiovascular Outcomes Subcommittee
The Cardiovascular Outcomes Subcommittee is charged with identifying key risk factors and measurements for cardiovascular outcomes; recommending procedures for measuring relevant cardiovascular variables; and establishing realistic costs of proposed measurements and procedures.

3.7.3.4 Growth Outcomes Subcommittee
The Growth Outcomes Subcommittee is charged with identifying key risk factors and measurements for growth outcomes; recommending procedures for measuring morbidity associated with poor growth; and establishing realistic costs of proposed measurements and procedures.

3.7.4 Study-wide Subcommittees
Study-wide subcommittees currently include a Data Management, Analysis, and Quality Control Subcommittee, a Training and Education/Recruitment and Retention Subcommittee and a Laboratory/Specimen Working Group.

3.7.4.1 Data Management, Analysis, and Quality Control Subcommittee
The charge of the Data Management, Analysis, and Quality Control Subcommittee is to provide recommendations to the SC with respect to the development and implementation of a web-based data management system, the analysis of data, and the measurement, processes, and procedures for quality control. This subcommittee will be responsible for the concatenation and linkage of all sources of data to comprehensively characterize the epidemiology of CKD in children. This subcommittee will be the central body for the methodological developments of data analysis procedures and for recommending appropriate data analysis methods including interpretation and limitations of inferences from the study data. KIDMAC will chair this subcommittee.

3.7.4.2 Training and Education/Recruitment and Retention Subcommittee
The charge of the Training and Education/Recruitment and Retention Subcommittee is to provide recommendations to the SC with respect to the training and certification of study staff, the development of educational materials for recruitment, and the development of procedures to enhance recruitment and retention of study participants. This subcommittee will be part of the coordinating activities of the data coordinating center and two clinical coordinating centers and will be chaired by the data coordinating center project director, Judith Jerry-Fluker.

3.7.4.3 Laboratory/Specimen Working Group
The charge of the Laboratory/Specimen Working Group is to provide recommendations to the SC with respect to the collection, handling and shipping of samples collected. This subcommittee is further charged with assisting in the development and ongoing revision of the data collection forms, the study protocol, and the Manual of Procedures related to the subcommittees' particular area.

3.8 Study Website

The study website for CKiD is located at https://statepi.jhsph.edu/ckid/. A website on the internet facilitates the transfer of information to the general public. A website also facilitates the interactions among the DCC, both clinical coordinating centers, and clinical sites. This study website will provide information on how investigators can propose studies using the platform provided by the CKiD and how they may obtain the public data tape. A password-protected administrative website contains: (1) a directory of all study personnel; (2) administrative forms; (3) the archive of study publications; (4) copies of all questionnaires and guidelines; and (5) discussion boards. A discussion board for the steering committee as well as each subcommittee offers a forum for investigators to circulate and archive information. For example, suggestions for form and protocol revisions are posted and discussed at scheduled conference calls.

3.9 Study Policies

3.9.1 Investigator Categories

The CKiD SC recognizes two categories of investigators. First, there are CKiD investigators (CKiD-I), who are defined by the SC as investigators named by each clinical coordinating center and the data coordinating center, as well as a representative from each NIH institute supporting the cooperative agreement. Second, there are external investigators (CKiD-E), who are defined as any investigator who does not meet the criteria to be a CKiD-I.

CKiD-I who cease to meet the definition of CKiD-I are external investigators. Such departing CKiD-I must submit a letter to the SC within six months of departure, requesting authorship on any papers in process at the date of departure. This letter must detail how the departing CKiD-I meets authorship criteria, as outlined in section 3.9.2.3 below.

3.9.2 Proposals for CKiD Studies

3.9.2.1 CKiD Study Proposal Form, Submission and Review

Requests to use data collected by CKiD must be completed using the CKiD study proposal form or “concept sheet” shown in Appendix B and available online at https://statepi.jhsph.edu/ckid/. Completed concept sheets should be emailed to the DCC to the attention of Judith Jerry-Fluker (jjerry@jhu.edu) for posting and SC review.

Investigators are encouraged to develop studies in conjunction with one or more of the scientific subcommittee members listed in Appendix A. Study proposals dealing with CKiD specific aims and associated hypotheses outlined in sections 1.2 and 1.3 will have priority in terms of study resources. In evaluating proposed studies, the SC will consider whether the proposed study would interfere with, compete or conflict with the conduct of the CKiD core protocol. Proposed studies may require external funding to cover costs incurred by the CKiD clinical coordinating centers, clinical sites, central laboratories, and KIDMAC.

Human subject’s considerations include a commitment to maintain the confidentiality of enrolled participants. Hence, individually identifiable data may not be released. If the proposed study requires the collection of additional data from participants that are not

covered in the original informed consent process, then a supplemental written informed consent must be obtained from every participant in the proposed study. If a separate consent form is required for the proposed study, a copy of a signed ancillary study consent form for each study participant must be included in the CKiD record. A data file tracking all signed ancillary consent forms must be maintained by the primary investigator and an electronic copy of that file must be sent to the DCC.

External investigators submitting a CKiD concept sheet must include a biosketch in NIH format, and are encouraged to team with a CKiD-I as a collaborator to facilitate the timely conduct of the proposed initiative and to appropriately place initiatives in the context of the overall study data. Data from cohort studies are complex and CKiD-E are encouraged to have a close liaison with a CKiD-I. Submission of a concept sheet requires (a) key personnel certified in the NIH OHSR or equivalent training course (b) a signed contract and (c) one CKiD participant enrolled in the main study.

Once submitted to the DCC, concept sheets will be placed on a password-protected electronic bulletin board. The SC will assign a Primary Reviewer (often referring to the appropriate scientific subcommittee) who will prepare a written critique of the concept sheet within two weeks, when possible. The SC will review all study proposals and written critiques on a semimonthly conference call with the Lead Investigator and Primary Reviewer invited to attend. This process will occur in a timely manner, attempting to provide feedback to the primary investigator within 4 weeks of submission. The DCC will inform the primary investigator of the status as: approved, rejected, or deferred (revision requested).

3.9.2.2 Approved CKiD Study Concept Sheets

If approved, the DCC will assign the concept sheet a study number in the form of c-YY-###, where “c” takes values 1, 2, 3 and 9 representing the primary investigator affiliated with the mid-west CCC, east-coast CCC, KIDMAC and external investigator, respectively; YY will represent the year; and ### will represent the sequential ID of the concept sheet. This study number will accompany any communications regarding the approved study. The primary investigator named on the concept sheet is responsible for: (1) successful and timely completion of the proposed study; (2) communicating with the DCC to initiate creation of analytical datasets, selection of repository specimens, and (if necessary) data analysis; and (3) provision of an annual written progress report to the CKiD SC. No data, information, or specimens will be released prior to the primary investigator providing a copy of local IRB approval to the DCC. Studies that have failed to demonstrate notable progress within one year from the date of approval, or where scientific misconduct has occurred, as judged by the SC, may have approval status revoked by the SC.

3.9.2.3 Writing Committees

The aim of the following publication policy is to ensure scientific quality and facilitate the production of novel research contributions based on data collected by CKiD. A secondary aim of this publication policy is to ensure a fair collaborative effort among CKiD-I and CKiD-E. The publication policy follows the JAMA guidelines for all issues not explicitly discussed herein.

A writing committee consists of four to nine investigators and its composition may vary according to whether the primary investigator is a CKiD-I or a CKiD-E. The primary investigator who is named on the concept sheet may either be the lead or senior author. If the primary investigator is a CKiD-I, the writing committee for the publication may include a total of up to nine members as follows: (a) up to two additional investigators from the site of the primary investigator whom also must be named on the concept sheet; (b) up to two investigators from each of the other two sites; and (c) up to two members from NIH or other major contributor to the publication (e.g., a laboratory collaborator). Failure of a SC voting member to name a study representative co-author within two weeks of study approval results in no co-author from the voting member's site. The writing committee for a revoked study is disbanded.

If the primary investigator is a CKiD-E, the writing committee may include the following: (a) additional members of the research team of the primary investigator; (b) up to one investigator from each of the three centers of the study; and (c) up to two members from NIH or other major collaborating center. In any case, studies reporting data at the core of the specific aims of the study should have at least one representative from each of the three sites of the study. Ancillary or secondary studies do not need to have a coauthor from each of the three sites of the study. In accordance with the responsibility of co-authorship in scientific publications, individuals should only be coauthors if they have substantially contributed to the manuscript. Each voting member of the SC reserves the right of not naming a member of the team as a coauthor. Such right is appropriate, for example, to not include authors in specialized methodological papers when there are no individuals with expertise at a particular center (e.g., a new genetics method).

The primary investigator is responsible for the completion of the manuscript, as well as the determination of authorship order. The primary investigator is also responsible for communicating significant problems or delays to the SC in a timely manner. Complete draft manuscripts should be submitted to the co-authors for substantive, methodological, and/or statistical review. All members of the writing committee must participate in the writing and/or review process, returning edited drafts within a two week period. In the event that a writing committee member disagrees with a revised manuscript, an attempt should be made within the writing committee to resolve the issue. If such an effort fails, the issue should be brought by the primary investigator to the SC. If a participant of the writing committee does not actively participate in the preparation of the manuscript including responding to analysis and manuscript drafts, then he/she may be removed from the writing committee.

After writing committee approval, the draft should be emailed to KIDMAC for SC approval prior to journal submission. A member of the SC will be assigned as the primary reviewer and will have a target date of two weeks to review the draft and bring comments before the SC by meeting or conference call for approval. Manuscripts must be approved by the SC prior to submission. Primary investigators are responsible for informing KIDMAC about the disposition of submitted manuscripts. If a manuscript is accepted for publication, the primary investigator must send a portable document format (.pdf) version of the published article to KIDMAC. If data analysis was not carried out at KIDMAC, the primary investigator is responsible for sending computer programs and associated data sets to KIDMAC.

3.9.2.4 Study Acknowledgment

All manuscripts derived from data collected by CKiD must include the following acknowledgment:

> Data in this manuscript were collected by the Chronic Kidney Disease in children prospective cohort study (CKiD) with clinical coordinating centers (Principal Investigators) at Children's Mercy Hospital and the University of Missouri – Kansas City (Bradley Warady, MD) and Children's Hospital of Philadelphia (Susan Furth, MD, Ph.D.), Central Biochemistry Laboratory (George Schwartz, MD) at the University of Rochester Medical Center, and data coordinating center at the Johns Hopkins Bloomberg School of Public Health (Alvaro Muñoz, Ph.D.) (U01-DK-66143, U01-DK-66174, U01-DK-82194, U01-DK-66116). The CKiD is funded by the National Institute of Diabetes and Digestive and Kidney Diseases, with additional funding from the National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute. The CKID website is located at https://statepi.jhsph.edu/ckid/.

4. STUDY METHODS

4.1 Study Design

The design of the CKiD study is a prospective, observational cohort of children with chronic kidney disease. Exposures will be measured at baseline and scheduled annual follow-up visits will permit the subsequent updating of the exposures in cohort participants. Outcomes will also be assessed at the annual visits and they include: measures of kidney function; neurocognitive function; markers of risk factors for cardiovascular disease; growth and other co-morbid conditions. The study will use the power of the cohort design with regularly scheduled visits at which markers of disease progression will be measured under standardized procedures. Levels and longitudinal changes in markers will constitute the primary outcomes. The study will collect data on clinical events with primary interest in ESRD and death. Such events will provide time-to-event data to determine heterogeneity of times to ESRD in children with mild to moderate chronic kidney disease.

4.2 Study Population

The CKiD study population will include three cohorts. Cohort 1 includes approximately 600 racially and ethnically diverse children, age 1-16 years old with mildly to moderately impaired kidney function, defined by an estimated GFR between 30 and 90 ml/min|1.73m^2 by the Schwartz formula (sGFR). Cohort 2 includes approximately 300 children with more mildly impaired kidney function, defined as an estimated GFR between 45 and 90 by the updated Schwartz formula (eGFR). In addition, Cohort 2 was compromised of approximately 150 children with glomerular disease and approximately 150 children with non-glomerular causes of disease. Cohort 3 will include 190 children with non-glomerular diagnosis and duration of kidney disease less than 5 years but age at enrollment could range from 6 months to 16 years old.

Table 4.2 describes the number of children in each stratum of age and estimated GFR that were recruited in Cohort 1. The high frequency of children with an estimated GFR between 40 and 59 ml/min|1.73m^2 (206) will empower the study to describe the heterogeneity of progression in children with renal insufficiency. Among the 276 children with an estimated GFR between 60 to 90, there will be a subset of non-progressors who will play the role of “controls” and can be expected to be followed for a longer period of time; in contrast, the highest frequency of fast progressors will be expected among those with GFR between 30 to 39 ml/min|1.73m^2 at baseline. The distribution by age is based on observed rates in the North American Pediatric Cooperative

Table 4.2 Recruitment by sGFR[a] and Age

	Age, yrs			
sGFR	1-4	5-10	11-16	Total
60-90	49	93	134	276
40-59	32	83	91	206
30-39	18	37	49	104
Total	99	213	274	586

[a] sGFR = (k x body length / serum creatinine)

where k=0.45, 0.55, 0.70 according to age-gender categories

Study [NAPRTCS 2002] CRI registry. In the NAPRTCS registry, 18% of the children are age 1 to 5, 52% are age 6 to 12, and 30% are age 11 to 16. In comparison, the age of the cohort will be stratified into the following three age groups: 1 to 4; 5 to 10; and 11 to 16 years. Therefore, the percentages have been adjusted to recruit a higher number of children in the oldest age group, 16%, 36% and 47%, respectively.

In Cohorts 1 and 2, children less than one year old were not enrolled; however, in cohort 3 we will focus on enrolling children close to their onset of kidney disease. Therefore, we will enroll children as young as 6 months old. The upper limit of 16 years was chosen to optimize follow-up for all subjects to be followed for at least four years, since the subjects would likely remain under the care of the pediatric nephrology centers enrolling patients.

Based on estimates from both CCCs, in Cohort 1 we expected 56% Caucasian, 24% African-American, 15% Hispanic, and 5% Asian, Pacific Islander, American Indian, or other, and we placed an upper limit of 65% for the percent of the cohort that would be Caucasian. In Cohort 1, 37% of children with glomerular disease were African-American. Since the study expected to enroll a higher proportion of children with glomerular disease in Cohort 2, it was also expected that there would be more African-American children enrolled resulting in more generalizable study population. However, there were similar percentages of African-Americans enrolled in both cohort, 23% and 20% respectively. In Cohort 3, we expect to enroll a similar percentage of African-Americans and we will place an upper limit of 65% for Caucasian enrollment. Also, based on estimates from the east coast CCC, we expect that overall 40% of the combined cohort will be female.

4.2.1 Inclusion Criteria

Determining eligibility is a multi-step process involving the review of medical information, participant interview, and conference with the participant's health care provider and the PI. Information collected on the Eligibility Form represents the first step in determining a participant's eligibility based on available information.

Eligibility for Cohort 1 was determined by obtaining two estimated GFR measurements, with a value between 30 to 90 ml/min|1.73m^2. The first measurement must be within the past six months and the second measurement within the past 18 months. Specifically, the GFR will be estimated using the Schwartz formula (GFR = kL/S_{Cr}), where k is 0.45 for males and females 12 months to 18 months; 0.55 for males between 19 months and 13 years (before 13th birthday) and females 19 months and older ; and 0.7 for males after 13th birthday. Tables 5.2.1a, 5.2.1b and 5.2.1c in the study recruitment section provide the interval of serum creatinine that would enable a child to participate according to his/her height. For example, males 13 years old and older whose height is 122 cm will be eligible to be included as participants if the S_{Cr} is between 1.1 (corresponding to a GFR of 90) and 2.8 mg/dl (corresponding to a GFR of 30).

Eligibility for Cohort 2 was determined by obtaining two estimated GFR measurements, with a value between 45 to 90 ml/min|1.73m^2. Similarly to Cohort 1, the first measurement must be within the past six months and the second measurement within the past 18 months. However, the GFR was estimated using the updated Schwartz

formula (eGFR = 41.3 [height / S_{Cr}]) for height measured in meters. If height is measured in centimeters (cm), then the formula is eGFR = 0.413 [height / S_{Cr}]. For Cohort 2, recruitment efforts were focused on enrolling an equal distribution of children with glomerular and non-glomerular disease.

Eligibility for Cohort 3 will be determined by having a Non-Glomerular diagnosis of CKD whose duration is less than 5 years at date of enrollment and age between 6 months to 16 years old. In order to assure that CKD is present, for specific non-glomerular diagnoses, we will require two or more of the following: 1) urine protein to creatinine ratio greater than 0.5 for children less than 2 years old, or urine protein to creatinine ratio greater than 0.2 for children 2 years of age and older; 2) hematuria (for at least 3 months); 3) evidence of renal tubular disorders; 4) abnormalities detected by kidney biopsy or imaging (bilateral disease or solitary kidney disease); 5) a serum creatinine measurement greater than 0.4mg/dL for children less than 2 years old, or, for children 2 years of age and older, an estimated Glomerular Filtration Rate (eGFR) less than 90 ml/min|1.73m^2 based on the updated Schwartz formula; or 6) hypertension defined by documented note in medical record, current treatment of hypertension, or blood pressure > 95th percentile on at least two occasions. Additionally, these conditions must have occurred after the initial 6 months of life (with the exception of abnormalities detected by kidney biopsy or imaging) and must not be secondary to a current or resolving episode of acute kidney injury. Since description of course to renal replacement therapy is of primary interest, children who are expected to receive renal replacement therapy within 6 months of date of enrollment will not be recruited. Eligible children must be willing to complete baseline and follow-up testing, and all procedures at scheduled annual visits for the duration of the study. Spanish-speaking children and children who are blind and/or deaf who meet the inclusion criteria will be eligible for study participation if they are able to complete either the neurocognitive or behavioral assessments of the neuropsychological component and all other study procedures. Since retention in a cohort study is of central importance, numerous efforts will be employed to include in the cohort children with the highest likelihood of participation in the study for the long term. Also, children can be included in the study only if they and their parents/legal guardians are willing and able to provide informed consent and assent.

In summary, the following conditions comprise the inclusion criteria:

- Age between 1 and 16 years (before 17th birthday) for Cohorts 1 and 2; age between 6 months and 16 years (before 17th birthday) for Cohort 3
- Estimated (based on S_{Cr}) Schwartz GFR between 30 and 90 ml/min|1.73m^2 for Cohort 1 OR an estimated GFR between 45 and 90 ml/min|1.73m^2 based on the updated Schwartz formula for Cohort 2
- Willingness and ability to provide informed consent and assent
- For Cohort 2, an equal distribution of children with glomerular and non-glomerular causes of disease were enrolled (i.e., 150 within each) and the study placed an upper limit of 60% for the percent of enrolled with non-glomerular disease.

- For Cohort 3, 190 children with non-glomerular diagnosis and duration of kidney disease less than 5 years will be enrolled.

  Patients with the non-glomerular diagnoses listed below that meet the initial criteria (i.e., duration of kidney disease less than 5 years, and age between 6 months and 16 years old) are eligible and do not have to meet additional criteria:
  - Branchio-oto-Renal Disease/Syndrome
  - Cystinosis
  - Medullary cystic disease/ juvenile nephronophthisis
  - Methylmalonic Acidemia
  - Oxalosis
  - Polycystic kidney disease (Autosomal recessive)

  However, all other patients with non-glomerular diagnoses will require at least two of the following conditions. All conditions except for abnormal imaging/biopsy must have occurred after the initial 6 months of life and must not be secondary to a current or resolving episode of Acute Kidney Injury (AKI):
    - significant proteinuria,
      - Age < 2 years old: urine protein to creatinine ratio > 0.5
      - Age ≥ 2 years old: urine protein to creatinine ratio > 0.2
    - hematuria (for at least 3 months),
    - evidence of renal tubular disorders,
    - abnormalities detected by kidney biopsy or imaging
    - abnormal kidney function
      - Age < 2 years old: serum creatinine > 0.4 mg/dL
      - Age ≥ 2 years old: eGFR < 90 ml/min|1.73m^2
        (eGFR=41.3 x height[meter]/creatinine[mg/dL])
    - Hypertension defined by one of the following:
      - Documented hypertension noted in the medical record by the physician
      - Current treatment of hypertension
      - Blood pressure > 95th percentile for age and gender on at least two occasions

4.2.2 Exclusion Criteria

Among the children who fulfill the inclusion criteria, certain medical conditions and/or the inability to assess exposures of interest will deem them ineligible. Specifically, the following conditions comprise the exclusion criteria:

- Renal, other solid organ, bone marrow or stem cell transplantation
- Dialysis treatment within the past three months
- Cancer diagnosis or HIV diagnosis/treatment within last twelve months
- Current pregnancy or pregnancy within past twelve months
- Inability to complete major data collection procedures
- Current enrollment in a randomized clinical trial in which the specific treatment is unknown
- Not fluent in English or Spanish
- Plans to move out of area of any participating CKiD site (Families can be transferred to another CKiD site if they move)
- History of structural heart disease
- Genetic syndromes involving the central nervous system (e.g., Downs syndrome)
- History of severe to profound mental retardation (i.e., IQ<40, significant impairment in adaptive function and/or inability to independently execute self-care skills)
- For cohort 3, children who are expected to receive renal replacement therapy within 6 months of date of enrollment will not be recruited.

4.2.3 Recruitment of Additional African-American Children

After reaching the original recruitment goal of 540 children, cohort 1 was comprised of a 15% African-American population. So the study continued to recruit an additional 60 African-American children, which resulted in a racial demographic of 23%. To accomplish the goal of recruiting more African-American children, the study targeted recruitment at a selected number of sites located in geographical areas with high percentages of minorities (i.e., Washington, DC, Brooklyn, NY, Chicago, IL) and encouraged sites to recruit African-Americans during Steering Committee and coordinator conference calls. In Cohort 2, targeted recruitment of additional African-Americans was not done. The study will monitor the recruitment of African-American and if necessary targeted recruitment at selected sites will be completed to ensure the study recruits a generalizable population of African-Americans.

5. RECRUITMENT/FOLLOW-UP

5.1 Overview of Recruitment

In Cohort 1, each Clinical Coordinating Center was committed to recruiting 300 participants into the CKiD Study. In Cohort 2, each was committed to recruiting 140. In Cohort 3, each CCC is committed to recruiting 95 participants. Recruitment sources and strategies will vary from site to site, but will most likely include computerized database searches, manual searches of medical records, referrals from health care providers, and patient panels of CKiD investigators. Investigators are encouraged to present the CKiD study to their colleagues as well as to discuss it with other health care providers, particularly pediatricians and nephrologists in their area. A patient brochure and study poster will describe the basic study objectives and information on how to join the study and can be used to recruit participants and remind clinical staff of the study. Further recruitment and referral information will be presented through advertisements in the National Kidney Foundation Newsletter "Family Focus", through posters and presentations at national scientific meetings of Pediatric Nephrology, and/or the website of the Kidney and Urology Foundation of America.

5.2 Recruitment Process

In Cohort 1, each clinical site identified potentially eligible participants, age 1-16 years with reduced kidney function based on an estimated GFR of 30-90 ml/min/1.73m². In Cohort 2, clinical sites identified eligible participants with an estimated GFR of 45-90 based on the updated Schwartz formula. In Cohort 3, clinical sites will identify eligible participants with duration of CKD less than 5 years and serum creatinine greater or equal to 0.5 mg/dl. Eligible participants will be identified via recruitment sources and strategies available at their particular site. These include, but are not limited to, automated laboratory database searches for eligible patients age 6 months to 16 years with reduced kidney function, referrals from physicians or specialty centers of potential participants, self-referral from potential participants who may respond to the study brochure or poster or hear about the study from relatives or friends. In contrast to the recruitment efforts of Cohort 1 where 78% of the cohort had non-glomerular disease, the recruitment process of Cohort 2 focused on enrolling an equal distribution of children with glomerular and non-glomerular disease. Specifically, it was expected that 50% of the children in Cohort 2 would have glomerular disease and the study placed an upper limit of 60% for the percent of enrolled with non-glomerular disease. When recruitment approached the upper limit, sites were notified that recruitment efforts should be focused on enrolling only children with glomerular disease. In Cohort 3, all children will have non-glomerular disease.

5.2.1 Identifying potential participants

In the recruitment efforts for Cohort 1, Tables 5.2.1a, 5.2.1b and 5.2.1c showed the ranges of S_{Cr} that correspond to a GFR between 30 and 90 ml/min|1.73m^2 for children of different genders and heights. The lower serum creatinine limit of the range corresponds to an estimated GFR of 90 ml/min|1.73m^2 and the higher limit corresponds to an estimated GFR of 30 ml/min|1.73m^2.

In Cohort 2, Table 5.2.1d showed the ranges of S_{Cr} that correspond to an estimated GFR between 45 and 90 based on the updated Schwartz bedside formula. Similarly to Cohort 1, the lower serum creatinine limit of the range corresponds to an estimated GFR of 90 ml/min|1.73m^2 and the higher limit corresponds to an estimated GFR of 45 ml/min|1.73m^2 and two estimated GFR measurements will be required for study enrollment. The first measurement must be within the past six months and the second measurement within the past 18 months.

Eligibility for Cohort 3 will be determined by having a non-glomerular diagnosis of CKD whose duration is less than 5 years at date of enrollment and age between 6 months to 16 years old. In order to assure that CKD is present, for specific non-glomerular diagnoses, at least two more conditions must be met as outlined in the inclusion criteria under section 4.2.1. One of the additional criteria is the presence of abnormal kidney function. Unlike Cohort 1 and 2, the presence of abnormal kidney function is an optional eligibility criteria for Cohort 3. If abnormal kidney function is not present, a child is still eligible if they meet at least two of the other conditions. For Cohort 3, abnormal kidney function is defined as having a serum creatinine measurement greater than 0.4mg/dL for children less than 2 years old, or, for children 2 years of age and older, an estimated GFR less than 90 ml/min|1.73m^2 based on the updated Schwartz formula. Table 5.2.1e shows the ranges of S_{Cr} that correspond to an estimated GFR ≤ 90 ml/min|1.73m^2 for children of different heights who are 2 years old and older.

Table 5.2.1a, MALES & FEMALES (12 months to 18 months)**

Height		SCr			Height		SCr			Height		SCr		
(cm)	(in)	**Low**	–	**High**	(cm)	(in)	**Low**	–	**High**	(cm)	(in)	**Low**	–	**High**
45	17.7	**0.23**	–	**0.67**	57	22.4	**0.29**	–	**0.85**	69	27.2	**0.35**	–	**1.03**
46	18.1	**0.23**	–	**0.69**	58	22.8	**0.29**	–	**0.87**	70	27.6	**0.35**	–	**1.05**
47	18.5	**0.24**	–	**0.70**	59	23.2	**0.30**	–	**0.99**	71	28.0	**0.36**	–	**1.06**
48	18.9	**0.24**	–	**0.72**	60	23.6	**0.30**	–	**0.90**	72	28.3	**0.36**	–	**1.08**
49	19.3	**0.25**	–	**0.73**	61	24.0	**0.31**	–	**0.91**	73	28.7	**0.37**	–	**1.09**
50	19.7	**0.25**	–	**0.75**	62	24.4	**0.31**	–	**0.93**	74	29.1	**0.37**	–	**1.11**
51	20.1	**0.26**	–	**0.76**	63	24.8	**0.32**	–	**0.94**	75	29.5	**0.38**	–	**1.12**
52	20.5	**0.26**	–	**0.78**	64	25.2	**0.32**	–	**0.96**	76	29.9	**0.38**	–	**1.14**
53	20.9	**0.27**	–	**0.79**	65	25.6	**0.33**	–	**0.97**	77	30.3	**0.39**	–	**1.15**
54	21.3	**0.27**	–	**0.81**	66	26.0	**0.33**	–	**0.99**	78	30.7	**0.39**	–	**1.17**
55	21.7	**0.28**	–	**0.82**	67	26.4	**0.34**	–	**1.00**	79	31.1	**0.40**	–	**1.18**
56	22.0	**0.28**	–	**0.84**	68	26.8	**0.34**	–	**1.02**	80	31.5	**0.40**	–	**1.20**

*Serum Creatinine Range is based on estimated GFR of 30-90 ml/min/1.73m^2
**before 19 months old.

IMPORTANT: For children between the age of 12 and 18 months, it is important that clinical sites contact their CCC to discuss the age and height of the child to ensure that the appropriate K value is used to obtain the most recent (within the last 6 months) and second (within the last 18 months) estimated GFR.

EXAMPLE: **13 month old**, **male** or **female** whose height is **57 cm** will be eligible if the S_{Cr} is between **0.29** and **0.85**. [S_{Cr} = .4 (eligible); S_{Cr} = .2 (ineligible)]

Table 5.2.1b, MALES (19 months to before 13th birthday) & FEMALES (19 months and older)

Height		SCr			Height		SCr			Height		SCr		
(cm)	(in)	**Low**	–	**High**	(cm)	(in)	**Low**	–	**High**	(cm)	(in)	**Low**	–	**High**
70	27.6	**0.43**	–	**1.28**	113	44.5	**0.69**	–	**2.07**	156	61.4	**0.95**	–	**2.86**
71	28.0	**0.43**	–	**1.30**	114	44.9	**0.70**	–	**2.09**	157	61.8	**0.96**	–	**2.87**
72	28.3	**0.44**	–	**1.32**	115	45.3	**0.70**	–	**2.10**	158	62.2	**0.97**	–	**2.89**
73	28.7	**0.45**	–	**1.33**	116	45.7	**0.71**	–	**2.12**	159	62.6	**0.97**	–	**2.91**
74	29.1	**0.45**	–	**1.35**	117	46.1	**0.72**	–	**2.14**	160	63.0	**0.98**	–	**2.93**
75	29.5	**0.46**	–	**1.37**	118	46.5	**0.72**	–	**2.16**	161	63.4	**0.98**	–	**2.95**
76	29.9	**0.46**	–	**1.39**	119	46.9	**0.73**	–	**2.18**	162	63.8	**0.99**	–	**2.97**
77	30.3	**0.47**	–	**1.41**	120	47.2	**0.73**	–	**2.20**	163	64.2	**1.00**	–	**2.98**
78	30.7	**0.48**	–	**1.43**	121	47.6	**0.74**	–	**2.21**	164	64.6	**1.00**	–	**3.00**
79	31.1	**0.48**	–	**1.44**	122	48.0	**0.75**	–	**2.23**	165	65.0	**1.01**		**3.02**
80	31.5	**0.49**	–	**1.46**	123	48.4	**0.75**	–	**2.25**	166	65.4	**1.01**	–	**3.04**
81	31.9	**0.50**	–	**1.48**	124	48.8	**0.76**	–	**2.27**	167	65.7	**1.02**	–	**3.06**
82	32.3	**0.50**	–	**1.50**	125	49.2	**0.76**	–	**2.29**	168	66.1	**1.03**	–	**3.08**
83	32.7	**0.51**	–	**1.52**	126	49.6	**0.77**	–	**2.31**	169	66.5	**1.03**	–	**3.09**
84	33.1	**0.51**	–	**1.54**	127	50.0	**0.78**	–	**2.32**	170	66.9	**1.04**	–	**3.11**
85	33.5	**0.52**	–	**1.55**	128	50.4	**0.78**	–	**2.34**	171	67.3	**1.05**	–	**3.13**
86	33.9	**0.53**	–	**1.57**	129	50.8	**0.79**	–	**2.36**	172	67.7	**1.05**	–	**3.15**
87	34.3	**0.53**	–	**1.59**	130	51.2	**0.79**	–	**2.38**	173	68.1	**1.06**	–	**3.17**
88	34.6	**0.54**	–	**1.61**	131	51.6	**0.80**	–	**2.40**	174	68.5	**1.06**	–	**3.19**
89	35.0	**0.54**	–	**1.63**	132	52.0	**0.81**	–	**2.42**	175	68.9	**1.07**	–	**3.20**
90	35.4	**0.55**	–	**1.65**	133	52.4	**0.81**	–	**2.43**	176	69.3	**1.08**	–	**3.22**
91	35.8	**0.56**	–	**1.66**	134	52.8	**0.82**	–	**2.45**	177	69.7	**1.08**	–	**3.24**
92	36.2	**0.56**	–	**1.68**	135	53.1	**0.83**	–	**2.47**	178	70.1	**1.09**	–	**3.26**
93	36.6	**0.57**	–	**1.70**	136	53.5	**0.83**	–	**2.49**	179	70.5	**1.09**	–	**3.28**
94	37.0	**0.57**	–	**1.72**	137	53.9	**0.84**	–	**2.51**	180	70.9	**1.10**	–	**3.30**
95	37.4	**0.58**	–	**1.74**	138	54.3	**0.84**	–	**2.53**	181	71.3	**1.11**	–	**3.31**
96	37.8	**0.59**	–	**1.76**	139	54.7	**0.85**	–	**2.54**	182	71.7	**1.11**	–	**3.33**
97	38.2	**0.59**	–	**1.77**	140	55.1	**0.86**	–	**2.56**	183	72.0	**1.12**	–	**3.35**
98	38.6	**0.60**	–	**1.79**	141	55.5	**0.86**	–	**2.58**	184	72.4	**1.12**	–	**3.37**
99	39.0	**0.61**	–	**1.81**	142	55.9	**0.87**	–	**2.60**	185	72.8	**1.13**	–	**3.39**
100	39.4	**0.61**	–	**1.83**	143	56.3	**0.87**	–	**2.62**	186	73.2	**1.14**	–	**3.41**
101	39.8	**0.62**	–	**1.85**	144	56.7	**0.88**	–	**2.64**	187	73.6	**1.14**	–	**3.42**
102	40.2	**0.62**	–	**1.87**	145	57.1	**0.89**	–	**2.65**	188	74.0	**1.15**	–	**3.44**
103	40.6	**0.63**	–	**1.88**	146	57.5	**0.89**	–	**2.67**	189	74.4	**1.16**	–	**3.46**
104	40.9	**0.64**	–	**1.90**	147	57.9	**0.90**	–	**2.69**	190	74.8	**1.16**	–	**3.48**
105	41.3	**0.64**	–	**1.92**	148	58.3	**0.90**	–	**2.71**	191	75.2	**1.17**	–	**3.50**
106	41.7	**0.65**	–	**1.94**	149	58.7	**0.91**	–	**2.73**	192	75.6	**1.17**	–	**3.52**
107	42.1	**0.65**	–	**1.96**	150	59.1	**0.92**	–	**2.75**	193	76.0	**1.18**	–	**3.53**
108	42.5	**0.66**	–	**1.98**	151	59.4	**0.92**	–	**2.76**	194	76.4	**1.19**	–	**3.55**
109	42.9	**0.67**	–	**1.99**	152	59.8	**0.93**	–	**2.78**	195	76.8	**1.19**	–	**3.57**
110	43.3	**0.67**	–	**2.01**	153	60.2	**0.94**	–	**2.80**	196	77.2	**1.20**	–	**3.59**
111	43.7	**0.68**	–	**2.03**	154	60.6	**0.94**	–	**2.82**	197	77.6	**1.20**	–	**3.61**
112	44.1	**0.68**	–	**2.05**	155	61.0	**0.95**	–	**2.84**	198	78.0	**1.21**	–	**3.63**

*Serum Creatinine Range is based on estimated GFR of 30-90 ml/min/1.73m^2

IMPORTANT: For children between the age of 19 and 30 months, it is important that clinical sites contact their CCC to discuss the age and height of the child to ensure that the appropriate K value is used to obtain the most recent (within the last 6 months) and second (within the last 18 months) estimated GFR.

EXAMPLE: **11 year old male** or **14 year old female** whose height is **114 cm** will be eligible if the S_{Cr} is between **0.70** and **2.09** [S_{Cr} = 0.9 (eligible); S_{Cr} = 0.6 (ineligible)

Table 5.2.1c, MALES after 13th birthday

Height		SCr		
(cm)	(in)	**Low**	–	**High**
100	39.4	**0.78**	–	**2.33**
101	39.8	**0.79**	–	**2.35**
102	40.2	**0.79**	–	**2.38**
103	40.6	**0.80**	–	**2.40**
104	41.0	**0.81**	–	**2.42**
105	41.3	**0.82**	–	**2.45**
106	41.7	**0.82**	–	**2.47**
107	42.0	**0.83**	–	**2.49**
108	42.5	**0.84**	–	**2.52**
109	43.0	**0.85**	–	**2.54**
110	43.3	**0.86**	–	**2.56**
111	43.7	**0.86**	–	**2.59**
112	44.0	**0.87**	–	**2.61**
113	44.5	**0.88**	–	**2.63**
114	45.0	**0.89**	–	**2.66**
115	45.3	**0.89**	–	**2.68**
116	45.7	**0.90**	–	**2.70**
117	46.0	**0.91**	–	**2.73**
118	46.5	**0.92**	–	**2.75**
119	47.0	**0.93**	–	**2.77**
120	47.2	**0.93**	–	**2.80**
121	47.6	**0.94**	–	**2.82**
122	48.0	**0.95**	–	**2.84**
123	48.4	**0.96**	–	**2.87**
124	49.0	**0.97**	–	**2.89**
125	49.2	**0.97**	–	**2.91**
126	49.6	**0.98**	–	**2.94**
127	50.0	**0.99**	–	**2.96**
128	50.4	**1.00**	–	**2.98**
129	50.8	**1.00**	–	**3.01**
130	51.0	**1.01**	–	**3.03**
131	51.6	**1.02**	–	**3.05**
132	52.0	**1.03**	–	**3.08**
133	52.4	**1.03**	–	**3.10**

Height		SCr		
(cm)	(in)	**Low**	–	**High**
134	52.8	**1.04**	–	**3.12**
135	53.0	**1.05**	–	**3.15**
136	53.5	**1.06**	–	**3.17**
137	54.0	**1.07**	–	**3.19**
138	54.3	**1.07**	–	**3.22**
139	54.7	**1.08**	–	**3.24**
140	55.0	**1.09**	–	**3.26**
141	55.5	**1.10**	–	**3.29**
142	56.0	**1.11**	–	**3.31**
143	56.3	**1.11**	–	**3.33**
144	56.7	**1.12**	–	**3.36**
145	57.0	**1.13**	–	**3.38**
146	57.5	**1.14**	–	**3.40**
147	58.0	**1.15**	–	**3.43**
148	58.3	**1.15**	–	**3.45**
149	58.7	**1.16**	–	**3.47**
150	59.0	**1.17**	–	**3.50**
151	59.4	**1.17**	–	**3.52**
152	60.0	**1.19**	–	**3.54**
153	60.2	**1.19**	–	**3.57**
154	60.6	**1.20**	–	**3.59**
155	61.0	**1.21**	–	**3.61**
156	61.4	**1.21**	–	**3.64**
157	62.0	**1.22**	–	**3.66**
158	62.2	**1.23**	–	**3.68**
159	62.6	**1.24**	–	**3.71**
160	63.0	**1.24**	–	**3.73**
161	63.4	**1.25**	–	**3.75**
162	63.8	**1.26**	–	**3.78**
163	64.0	**1.26**	–	**3.80**
164	64.6	**1.28**	–	**3.82**
165	65.0	**1.28**	–	**3.85**
166	65.4	**1.29**	–	**3.87**

Height		SCr		
(cm)	(in)	**Low**	–	**High**
167	65.7	**1.30**	–	**3.89**
168	66.0	**1.30**	–	**3.92**
169	66.5	**1.31**	–	**3.94**
170	67.0	**1.32**	–	**3.96**
171	67.3	**1.33**	–	**3.99**
172	67.7	**1.34**	–	**4.01**
173	68.0	**1.34**	–	**4.03**
174	68.5	**1.35**	–	**4.06**
175	69.0	**1.36**	–	**4.08**
176	69.3	**1.37**	–	**4.10**
177	69.7	**1.38**	–	**4.13**
178	70.0	**1.38**	–	**4.15**
179	70.5	**1.39**	–	**4.17**
180	70.9	**1.40**	–	**4.20**
181	71.3	**1.41**	–	**4.22**
182	71.7	**1.42**	–	**4.24**
183	72.0	**1.42**	–	**4.27**
184	72.4	**1.43**	–	**4.29**
185	72.8	**1.44**	–	**4.31**
186	73.2	**1.45**	–	**4.34**
187	73.6	**1.45**	–	**4.36**
188	74.0	**1.46**	–	**4.38**
189	74.4	**1.47**	–	**4.41**
190	74.8	**1.48**	–	**4.43**
191	75.2	**1.49**	–	**4.45**
192	75.6	**1.49**	–	**4.48**
193	76.0	**1.50**	–	**4.50**
194	76.4	**1.51**	–	**4.52**
195	76.8	**1.52**	–	**4.55**
196	77.2	**1.52**	–	**4.57**
197	77.6	**1.53**	–	**4.59**
198	78.0	**1.54**	–	**4.62**
199	78.3	**1.55**	–	**4.64**

*Serum Creatinine Range is based on estimated GFR of 30-90 ml/min/1.73m^2

EXAMPLE: **15 year old male** whose height is **134 cm** will be eligible if the S_{Cr} is between **1.04** and **3.12** [S_{Cr} = 1.3 (eligible); S_{Cr} = 1.0 (ineligible)]

Table 5.2.1d, Eligible SCr ranges* by height based for Cohort 2

Height		SCr			Height		SCr			Height		SCr			Height		SCr		
(cm)	(in)	**Low**	–	**High**	(cm)	(in)	**Low**	–	**High**	(cm)	(in)	**Low**	–	**High**	(cm)	(in)	**Low**	–	**High**
50	19.7	**0.23**	–	**0.46**	85	33.5	**0.39**	–	**0.78**	120	47.2	**0.55**	–	**1.10**	155	61.0	**0.71**	–	**1.42**
51	20.1	**0.23**	–	**0.46**	86	33.9	**0.39**	–	**0.78**	121	47.6	**0.56**	–	**1.12**	156	61.4	**0.72**	–	**1.44**
52	20.5	**0.24**	–	**0.48**	87	34.3	**0.40**	–	**0.80**	122	48.0	**0.56**	–	**1.12**	157	61.8	**0.72**	–	**1.44**
53	20.9	**0.24**	–	**0.48**	88	34.6	**0.40**	–	**0.80**	123	48.4	**0.56**	–	**1.12**	158	62.2	**0.73**	–	**1.46**
54	21.3	**0.25**	–	**0.50**	89	35.0	**0.41**	–	**0.82**	124	48.8	**0.57**	–	**1.14**	159	62.6	**0.73**	–	**1.46**
55	21.7	**0.25**	–	**0.50**	90	35.4	**0.41**	–	**0.82**	125	49.2	**0.57**	–	**1.14**	160	63.0	**0.73**	–	**1.46**
56	22.0	**0.26**	–	**0.52**	91	35.8	**0.42**	–	**0.84**	126	49.6	**0.58**	–	**1.16**	161	63.4	**0.74**	–	**1.48**
57	22.4	**0.26**	–	**0.52**	92	36.2	**0.42**	–	**0.84**	127	50.0	**0.58**	–	**1.16**	162	63.8	**0.74**	–	**1.48**
58	22.8	**0.27**	–	**0.54**	93	36.6	**0.43**	–	**0.86**	128	50.4	**0.59**	–	**1.18**	163	64.2	**0.75**	–	**1.50**
59	23.2	**0.27**	–	**0.54**	94	37.0	**0.43**	–	**0.86**	129	50.8	**0.59**	–	**1.18**	164	64.6	**0.75**	–	**1.50**
60	23.6	**0.28**	–	**0.56**	95	37.4	**0.44**	–	**0.88**	130	51.2	**0.60**	–	**1.20**	165	65.0	**0.76**	–	**1.52**
61	24.0	**0.28**	–	**0.56**	96	37.8	**0.44**	–	**0.88**	131	51.6	**0.60**	–	**1.20**	166	65.4	**0.76**	–	**1.52**
62	24.4	**0.28**	–	**0.56**	97	38.2	**0.45**	–	**0.90**	132	52.0	**0.61**	–	**1.22**	167	65.7	**0.77**	–	**1.54**
63	24.8	**0.29**	–	**0.58**	98	38.6	**0.45**	–	**0.90**	133	52.4	**0.61**	–	**1.22**	168	66.1	**0.77**	–	**1.54**
64	25.2	**0.29**	–	**0.58**	99	39.0	**0.45**	–	**0.90**	134	52.8	**0.61**	–	**1.22**	169	66.5	**0.78**	–	**1.56**
65	25.6	**0.30**	–	**0.60**	100	39.4	**0.46**	–	**0.92**	135	53.1	**0.62**	–	**1.24**	170	66.9	**0.78**	–	**1.56**
66	26.0	**0.30**	–	**0.60**	101	39.8	**0.46**	–	**0.92**	136	53.5	**0.62**	–	**1.24**	171	67.3	**0.78**	–	**1.56**
67	26.4	**0.31**	–	**0.62**	102	40.2	**0.47**	–	**0.94**	137	53.9	**0.63**	–	**1.26**	172	67.7	**0.79**	–	**1.58**
68	26.8	**0.31**	–	**0.62**	103	40.6	**0.47**	–	**0.94**	138	54.3	**0.63**	–	**1.26**	173	68.1	**0.79**	–	**1.58**
69	27.2	**0.32**	–	**0.64**	104	40.9	**0.48**	–	**0.96**	139	54.7	**0.64**	–	**1.28**	174	68.5	**0.80**	–	**1.60**
70	27.6	**0.32**	–	**0.64**	105	41.3	**0.48**	–	**0.96**	140	55.1	**0.64**	–	**1.28**	175	68.9	**0.80**	–	**1.60**
71	28.0	**0.33**	–	**0.66**	106	41.7	**0.49**	–	**0.98**	141	55.5	**0.65**	–	**1.30**	176	69.3	**0.81**	–	**1.62**
72	28.3	**0.33**	–	**0.66**	107	42.1	**0.49**	–	**0.98**	142	55.9	**0.65**	–	**1.30**	177	69.7	**0.81**	–	**1.62**
73	28.7	**0.33**	–	**0.66**	108	42.5	**0.50**	–	**1.00**	143	56.3	**0.66**	–	**1.32**	178	70.1	**0.82**	–	**1.64**
74	29.1	**0.34**	–	**0.68**	109	42.9	**0.50**	–	**1.00**	144	56.7	**0.66**	–	**1.32**	179	70.5	**0.82**	–	**1.64**
75	29.5	**0.34**	–	**0.68**	110	43.3	**0.50**	–	**1.00**	145	57.1	**0.67**	–	**1.34**	180	70.9	**0.83**	–	**1.66**
76	29.9	**0.35**	–	**0.70**	111	43.7	**0.51**	–	**1.02**	146	57.5	**0.67**	–	**1.34**	181	71.3	**0.83**	–	**1.66**
77	30.3	**0.35**	–	**0.70**	112	44.1	**0.51**	–	**1.03**	147	57.9	**0.67**	–	**1.34**	182	71.7	**0.84**	–	**1.68**
78	30.7	**0.36**	–	**0.72**	113	44.5	**0.52**	–	**1.04**	148	58.3	**0.68**	–	**1.36**	183	72.0	**0.84**	–	**1.68**
79	31.1	**0.36**	–	**0.72**	114	44.9	**0.52**	–	**1.04**	149	58.7	**0.68**	–	**1.36**	184	72.4	**0.84**	–	**1.68**
80	31.5	**0.37**	–	**0.74**	115	45.3	**0.53**	–	**1.06**	150	59.1	**0.69**	–	**1.38**	185	72.8	**0.85**	–	**1.70**
81	31.9	**0.37**	–	**0.74**	116	45.7	**0.53**	–	**1.06**	151	59.4	**0.69**	–	**1.38**	186	73.2	**0.85**	–	**1.70**
82	32.3	**0.38**	–	**0.76**	117	46.1	**0.54**	–	**1.08**	152	59.8	**0.70**	–	**1.40**	187	73.6	**0.86**	–	**1.72**
83	32.7	**0.38**	–	**0.76**	118	46.5	**0.54**	–	**1.08**	153	60.2	**0.70**	–	**1.40**	188	74.0	**0.86**	–	**1.72**
84	33.1	**0.39**	–	**0.78**	119	46.9	**0.55**	–	**1.10**	154	60.6	**0.71**	–	**1.40**	189	74.4	**0.87**	–	**1.74**

*Serum Creatinine Range is based on estimated GFR of 45-90 ml/min/1.73m^2

Table 5.2.1e, Eligible SCr ranges* by height based for Cohort 3 children 2 years old or older

Height		SCr		Height		SCr		Height		SCr		Height		SCr
(cm)	(in)	(mg/dL)		(cm)	(in)	(mg/dL)		(cm)	(in)	(mg/dL)		(cm)	(in)	(mg/dL)
50	19.7	**≥ 0.23**		85	33.5	**≥ 0.39**		120	47.2	**≥ 0.55**		155	61.0	**≥ 0.71**
51	20.1	**≥ 0.23**		86	33.9	**≥ 0.39**		121	47.6	**≥ 0.56**		156	61.4	**≥ 0.72**
52	20.5	**≥ 0.24**		87	34.3	**≥ 0.40**		122	48.0	**≥ 0.56**		157	61.8	**≥ 0.72**
53	20.9	**≥ 0.24**		88	34.6	**≥ 0.40**		123	48.4	**≥ 0.56**		158	62.2	**≥ 0.73**
54	21.3	**≥ 0.25**		89	35.0	**≥ 0.41**		124	48.8	**≥ 0.57**		159	62.6	**≥ 0.73**
55	21.7	**≥ 0.25**		90	35.4	**≥ 0.41**		125	49.2	**≥ 0.57**		160	63.0	**≥ 0.73**
56	22.0	**≥ 0.26**		91	35.8	**≥ 0.42**		126	49.6	**≥ 0.58**		161	63.4	**≥ 0.74**
57	22.4	**≥ 0.26**		92	36.2	**≥ 0.42**		127	50.0	**≥ 0.58**		162	63.8	**≥ 0.74**
58	22.8	**≥ 0.27**		93	36.6	**≥ 0.43**		128	50.4	**≥ 0.59**		163	64.2	**≥ 0.75**
59	23.2	**≥ 0.27**		94	37.0	**≥ 0.43**		129	50.8	**≥ 0.59**		164	64.6	**≥ 0.75**
60	23.6	**≥ 0.28**		95	37.4	**≥ 0.44**		130	51.2	**≥ 0.60**		165	65.0	**≥ 0.76**
61	24.0	**≥ 0.28**		96	37.8	**≥ 0.44**		131	51.6	**≥ 0.60**		166	65.4	**≥ 0.76**
62	24.4	**≥ 0.28**		97	38.2	**≥ 0.45**		132	52.0	**≥ 0.61**		167	65.7	**≥ 0.77**
63	24.8	**≥ 0.29**		98	38.6	**≥ 0.45**		133	52.4	**≥ 0.61**		168	66.1	**≥ 0.77**
64	25.2	**≥ 0.29**		99	39.0	**≥ 0.45**		134	52.8	**≥ 0.61**		169	66.5	**≥ 0.78**
65	25.6	**≥ 0.30**		100	39.4	**≥ 0.46**		135	53.1	**≥ 0.62**		170	66.9	**≥ 0.78**
66	26.0	**≥ 0.30**		101	39.8	**≥ 0.46**		136	53.5	**≥ 0.62**		171	67.3	**≥ 0.78**
67	26.4	**≥ 0.31**		102	40.2	**≥ 0.47**		137	53.9	**≥ 0.63**		172	67.7	**≥ 0.79**
68	26.8	**≥ 0.31**		103	40.6	**≥ 0.47**		138	54.3	**≥ 0.63**		173	68.1	**≥ 0.79**
69	27.2	**≥ 0.32**		104	40.9	**≥ 0.48**		139	54.7	**≥ 0.64**		174	68.5	**≥ 0.80**
70	27.6	**≥ 0.32**		105	41.3	**≥ 0.48**		140	55.1	**≥ 0.64**		175	68.9	**≥ 0.80**
71	28.0	**≥ 0.33**		106	41.7	**≥ 0.49**		141	55.5	**≥ 0.65**		176	69.3	**≥ 0.81**
72	28.3	**≥ 0.33**		107	42.1	**≥ 0.49**		142	55.9	**≥ 0.65**		177	69.7	**≥ 0.81**
73	28.7	**≥ 0.33**		108	42.5	**≥ 0.50**		143	56.3	**≥ 0.66**		178	70.1	**≥ 0.82**
74	29.1	**≥ 0.34**		109	42.9	**≥ 0.50**		144	56.7	**≥ 0.66**		179	70.5	**≥ 0.82**
75	29.5	**≥ 0.34**		110	43.3	**≥ 0.50**		145	57.1	**≥ 0.67**		180	70.9	**≥ 0.83**
76	29.9	**≥ 0.35**		111	43.7	**≥ 0.51**		146	57.5	**≥ 0.67**		181	71.3	**≥ 0.83**
77	30.3	**≥ 0.35**		112	44.1	**≥ 0.51**		147	57.9	**≥ 0.67**		182	71.7	**≥ 0.84**
78	30.7	**≥ 0.36**		113	44.5	**≥ 0.52**		148	58.3	**≥ 0.68**		183	72.0	**≥ 0.84**
79	31.1	**≥ 0.36**		114	44.9	**≥ 0.52**		149	58.7	**≥ 0.68**		184	72.4	**≥ 0.84**
80	31.5	**≥ 0.37**		115	45.3	**≥ 0.53**		150	59.1	**≥ 0.69**		185	72.8	**≥ 0.85**
81	31.9	**≥ 0.37**		116	45.7	**≥ 0.53**		151	59.4	**≥ 0.69**		186	73.2	**≥ 0.85**
82	32.3	**≥ 0.38**		117	46.1	**≥ 0.54**		152	59.8	**≥ 0.70**		187	73.6	**≥ 0.86**
83	32.7	**≥ 0.38**		118	46.5	**≥ 0.54**		153	60.2	**≥ 0.70**		188	74.0	**≥ 0.86**
84	33.1	**≥ 0.39**		119	46.9	**≥ 0.55**		154	60.6	**≥ 0.71**		189	74.4	**≥ 0.87**

*Serum Creatinine Range correspond to an eGFR ≤ 90 ml/min|1.73m^2 for children of different heights who are ≥ 2 years old

EXAMPLE: **3 year old** whose height is **84 cm** will be eligible if the S_{Cr} is ≥ **0.39**
[S_{Cr} = 0.41 (eligible); S_{Cr} = 0.22 (ineligible)]

5.2.2 Honorarium to Children and Family for Study Participation

Families will be provided with an honorarium at the time of each visit to offset expenses associated with participation in the study (e.g., sibling childcare, transportation, meals). Each year, the participating child may be given a small gift, such as a gift certificate, and sent a birthday card during the year as a reminder of the study. Holiday cards may also be sent to the families as a token of appreciation for their participation.

5.3 Retention Strategies

Retention of participants is central to the internal validity of the study and will be a high priority of the investigators and staff. A key element is a pleasant, attentive and responsive staff that provides a reasonably flexible visit schedule. Other clinical site features that promote high retention rates include: local tracking systems; frequent staff meetings; free and convenient parking (if applicable); personal contacts through holiday cards, and small gifts; and modest honorarium for participation.

5.3.1 Participant Withdrawal

It is anticipated that over the course of the study CKiD participants may withdraw from the study or develop conditions which will make them ineligible to continue study participation like cancer diagnosis. Exiting the study may occur officially by formal notification from the participant to the investigator, or unofficially when a participant cannot be reached via the usual methods of contact. Every effort will be made to acquire complete data on all participants. Centers may offer inducements to participants who drop-out or relocate in the form of additional travel reimbursement or referral to another CKiD clinical site that may be closer in return for their continued participation.

5.4 Follow-up Schedule

Approximately six hundred (600) children were enrolled over a four-year period in Cohort 1. In Cohort 2, approximately 300 children were enrolled over a two-year period. In Cohort 3, an additional 190 are expected to be enrolled. Participants enrolled in Cohort 2 followed the same contact pattern as Cohort 1. Participants were scheduled to return within 6 months of the baseline GFR assessment, depending on the age of the child and then annually for in-person follow-up visits for approximately 13 years in CKiD (i.e., through V15). Except for the GFR assessment, the neuro battery and some of the cardiovascular measurements, Cohort 3 will follow a similar contact pattern as the other cohorts. GFR assessment will be optional in cohort 3. These study visits are intended to be completed on an out-patient basis. In order to provide flexibility when scheduling study visits, each study visit may be scheduled during varying time periods. Specifically, V1a will be scheduled within one (1) year after the eligibility form is completed. V1b will be scheduled within 6 months but no more than one (1) year after V1a. The subsequent follow-up visits will be scheduled as follows:

- the first annual follow-up visit (V2) will occur one (1) year after V1a, plus or minus one month. However, if the visit is difficult to schedule, the visit can also be scheduled no more than two (2) years after V1a.
- Visit 3 will be scheduled two (2) years (± one month) after V1a or no more than three (3) years after V1a for visits that are difficult to schedule.
- Visit 4 will be scheduled three (3) years (± one month) after V1a or no more than four (4) years after V1a for visits that are difficult to schedule.

- Visit 5 will be scheduled four (4) years (± one month) after V1a or no more than five (5) years after V1a for visits that are difficult to schedule.
- Visit 6 will be scheduled five (5) years (± one month) after V1a or no more than six (6) years after V1a for visits that are difficult to schedule.
- Visit 7 will be scheduled six (6) years (± one month) after V1a or no more than seven (7) years after V1a for visits that are difficult to schedule.
- Visit 8 will be scheduled seven (7) years (± one month) after V1a or no more than eight (8) years after V1a for visits that are difficult to schedule.
- Visit 9 will be scheduled eight (8) years (± one month) after V1a or no more than nine (9) years after V1a for visits that are difficult to schedule.
- Visit 10 will be scheduled nine (9) years (± one month) after V1a or no more than ten (10) years after V1a for visits that are difficult to schedule.
- Visit 11 will be scheduled ten (10) years (± one month) after V1a or no more than eleven (11) years after V1a for visits that are difficult to schedule.
- Visit 12 will be scheduled eleven (11) years (± one month) after V1a or no more than twelve (12) years after V1a for visits that are difficult to schedule.
- Visit 13 will be scheduled twelve (12) years (± one month) after V1a or no more than thirteen (13) years after V1a for visits that are difficult to schedule.
- Visit 14 will be scheduled thirteen (13) years (± one month) after V1a or no more than fourteen (14) years after V1a for visits that are difficult to schedule.
- If the ECHO, Vascular Tests, Ambulatory Blood Pressure Monitoring (ABPM), cardiac MRI and Neurocognitive testing data cannot be obtained during the child's scheduled study visit, these measurements should be scheduled within one month of the scheduled visit. In the event that the ABPM device is not initiated within one month of the visit, the site should attempt to obtain the Mabis Medic auscultatory blood pressure measurements at the time the ABPM device is initiated. If the site is unable to obtain the auscultatory blood pressure measurements at the time the ABPM device is initiated, the site should contact their respective CCC for further instructions. Similarly, if the site is unable to reschedule the ECHO, Vascular Tests, cardiac MRI or Neurocognitive testing within one month of the scheduled visit, the site should contact their respective CCC for further instructions.

5.4.1 Contact Pattern and Time on Study and Calendar as Time Scales

The structure of the contact pattern has been dictated by the scientific aims of the study, whereby kidney function (measured by iohexol-based GFR) is the outcome for specific aim 1 and it is the exposure for specific aims 2, 3 and 4, whose objectives are to elucidate how changes in kidney function have deleterious effects on neurocognitive function, profile of risk factors for cardiovascular disease and growth failure. The objective of annual follow-up visits will be to collect information on exposures; measure kidney disease progression; assess cardiovascular risk factors, neurocognitive impairment and growth failure; determine health care utilization patterns; and assess the occurrence of clinical events related to the primary outcomes since last contact. Updated contact information will be obtained during the annual visits. Rescheduling visits will be decided by the clinical site's principal investigator on a case by case basis. For example, if a child is sick or dehydrated at the scheduled study visit, the clinical site

may decide to reschedule the visit. Clinical sites will inform their CCC when study visits are rescheduled.

Since, recruitment will occur at multiple sites, it is important that we develop a system so that the participant's identification number (study ID) will automatically indicate which site the child was enrolled. To accomplish this, we are planning to implement a system of study IDs. Specifically, the first digit will be the value "1" indicating enrollment in Cohort 1, "2" indicating enrollment in Cohort 2 and "3" indicating enrollment in Cohort 3. This will be followed by two digits indicating the site, such that values between "01" to "49" will be reserved for the sites in the mid-west CCC and the values "50" to "99" will identify the sites in the east-coast CCC. Finally, the last three digits will be reserved for the sequence of the participant in a given clinical site. For example, ID 1-17-012 will correspond to the 12th participant enrolled in site 17 of mid-west CCC. However, if the child relocates to another clinical site, the same study ID will follow the participant.

Table 5.4.1a depicts the contact pattern and the corresponding data to be obtained at baseline and at each annual follow-up visit. Specifically, the baseline visit will be comprised of two components: V1a and V1b. The first component of the baseline visit (V1a) will occur during the child's initial visit to the clinical site which will include procedures to obtain an iohexol-based GFR measurement. For the purpose of obtaining baseline data on neurocognitive function and growth, the second component of the baseline visit (V1b) will occur within 3 months after the first baseline visit for children between 1 and 3 years of age, and will occur within 6 months for children over the age of 3. The one to six month lag between the two components of visit one is necessary because the procedures needed to measure the GFR do not provide an environment conducive to an unbiased assessment of some of the neurocognitive tests.

Table 5.4.1a Measurements with Time-on-Study as Time Scale Science and Analysis

Topic	Variable	Year							
		0	1		2	3	4/ 8/12	6/ 10/14	5/7	9/11 13/15
		Pre-V	V1a	V1b	V2	V3	V4/ V8/V12	V6/ V10/V14	V5/V7	V9/V11/ V13/V15
	Eligibility Form (Inclusion & Exclusion Criteria)	♦								
	Consent Form and Study Brochure	♦								
	Family Information	♦	♦	♦	♦	♦	♦	♦	♦	♦
Kidney	Iohexol-based GFR[a]		X		X		X	X		
	Cystatin C		X		X	X	X	X	X	X
	Serum Creatinine		X		X	X	X	X	X	X
	Central Renal Panel		X		X	X	X	X	X	X
	Central Uric Acid[b]		X		X	X	X	X	X	X
	Central Urine Creatinine and Protein		X		X	X	X	X	X	X
	Central Urine Albumin		X		X	X	X	X	X	X
	Local Complete Blood Count		X		X	X	X	X	X	X
	Local Pregnancy Tests[c]		X		X	X	X	X	X	X
	Local Renal Panel		X		X	X	X	X	X	X
	Local Urine Creatinine and Urine Protein[d]		X		X	X	X	X	X	X
Cardiovascular	Clinical Blood Pressure (centrally calibrated)		■	■	■	■	■	■	■	■
	Clinical Blood Pressure (locally measured)		■	■	■	■	■	■	■	■
	Lipid Profile				■		■	■		
	Ambulatory Blood Pressure Monitoring				■		■	■		
	Echocardiography[e]				■			■		
	Carotid Intima-Media Thickness[e,f]				■			■		
	Vascular Tests[g]				■		■	■		
	Home Blood Pressure Monitoring[h]				■	■	■	■	■	■
	Cardiac Magnetic Resonance Imaging (MRI)[i]				■					
Neurocognitive	Pediatric Quality of Life			▲	▲	▲	▲	▲	▲	▲
	Cognitive and Development Assessments			▲		▲			▲	
	Behavioral Assessments			▲		▲			▲	▲
	NIH Toolbox Cognition Tests[j]			▲		▲			▲	▲
	NIH Toolbox Emotion Tests[j]			▲		▲			▲	▲
Growth	Height/Length and Weight		●	●	●	●	●	●	●	●
	Head Circumference		●	●	●	●	●	●	●	●
	Mid-Arm Circumference[k]		●	●	●	●	●	●	●	●
	Waist and Hip Circumferences[l]		●	●	●	●	●	●	●	●
	Tanner Stage		●		●	●	●	●	●	●
	Physical Activity Monitoring[m]			●	●	●	●	●	●	●
	Intact Parathyroid Hormone (iPTH)			●		●			●	●
	High Sensitivity CRP (hsCRP)			●		●			●	●
	Vitamin D			●		●			●	●
	Fibroblast Growth Factor-23 (FGF-23)			●		●			●	●
	Grip Strength[n]					●			●	●

[a] **Iohexol GFR**: Iohexol GFR was measured on all Cohort 1 and 2 participants. As of June 2016 amendment, iGFR is measured on a subset of Cohort 1 and 2. In Cohort 3, iGFR will be optional.
[b] **Cohorts 2 & 3**: For Cohorts 2 & 3, these tests will be measured at baseline and annual visits. For Cohort 1, the measurements of these tests were initiated at follow-up.
[c] **Pregnancy Tests**: Pregnancy tests will be performed on females of child bearing potential. Childbearing potential occurs when the female has reached menarche.
[d] **Local Urine Creatinine and Urine Protein**: Clinical sites requiring immediate results will perform urine creatinine and urine protein tests at their local laboratory in addition to the tests sent to CBL.
[e] **ECHO and Carotid IMT**: Performed at V2 and every four (4) years thereafter.
[f] **Carotid IMT**: At selected sites, sub-set of Cohorts 1 and 2 will have carotid IMT performed (N=100). In Cohort 3, the participants who are 5 years old and older will have carotid IMT performed.
[g] **Vascular Tests**: At selected sites, sub-set of Cohorts 1 and 2 will have vascular tests performed. In Cohort 3, the participants who are 5 years old and older will have vascular tests performed.
[h] **Home Blood Pressure Monitor**: At selected sites, sub-set of the entire cohort will have home blood pressure monitoring.
[i] **Cardiac MRI**: Sub-set of the entire cohort with a high probability of reaching ESRD will have cardiac MRI performed.
[j] **NIH Toolbox Tests**: At selected sites, sub-set of Cohort participants who are 3 years old and older will complete NIH toolbox texts.
[k] **Mid-Arm Circumference**: Mid-arm circumference will be measured at every study visit for the entire cohort.
[l] **Waist and Hip Circumferences**: Waist and Hip circumference will be measured at every study visit for the entire cohort.
[m] **Physical Activity Monitor**: At selected sites, sub-set of the entire cohort will have physical activity monitoring
[n] **Grip Strengh**: Grip strength will be measured in participants 6 years old and older.

As depicted in the table, markers related to the four specific aims will be measured every year (e.g., serum creatinine, Cystatin C, standardized clinical blood pressure obtained with a uniformed centrally-calibrated device, pediatric quality of life, height and weight). Except for the key variables of GFR, markers in the renal panel and cystatin C, which will be measured in the first two years, the core markers of kidney function and cardiovascular markers will be measured every two years on even years of follow-up. As illustrated in the table, GFR will be measured annually during the first two years and then every two years thereafter. For all children in Cohorts 1 and 2, two estimated GFR measurements were required for study enrollment; however, Cohort 3 will require a non-glomerular kidney disease diagnosis, and depending on the primary diagnosis will also require at least two other documented conditions (proteinuria, hematuria, renal tubular disorder, abnormalities detected by kidney biopsy of imaging, abnormal kidney function, or hypertension) not related to an acute kidney injury. In addition, at the visits where iohexol-based GFR and serum creatinine (S_{Cr}) will be concurrently available, this data will provide the elements to develop an internally valid formula to estimate GFR from S_{Cr}. With such a formula, during the visits in which only S_{Cr} will be available, the GFR can be estimated. Hence, with the combination of estimated and observed GFR data, the study will have annual GFR data for comprehensive longitudinal data analysis. Moreover, the two values of GFR that are measured one year apart during the first two years in the study for each participant will provide an assessment of short-term changes (i.e., GFR in year two – GFR in year one) early in the study and, in the long term, will provide a robust baseline assessment of the GFR (i.e., (GFR in year one + GFR in year two)/2) for this cohort of children.

The cardiovascular component will be implemented after the second year and every four (4) years thereafter. The cardiovascular outcomes will be measured while the participants wait for their blood to be drawn for GFR measuring. The same temporality of GFR levels and changes preceding the cardiovascular data (i.e., ECHO) will be provided by our proposed design. The only limitation for the study is that, for Cohort 2, half of the cohort will have only one assessment of cardiovascular risk factors by 2018.

The core markers of neurocognitive function and growth will be measured in the odd years from the third year on. A salient feature of the proposed contact pattern is that the assessment of neurocognitive function will not be perturbed by the requirements of the GFR protocol. The pattern outlined in the table will also be conducive to assessing the impact of the changes in GFR on the changes in neurocognitive function. Specifically, the changes in GFR between year 1 (0 to 12 months) and year 2 could be predictive of the changes in neurocognitive function between year 1 (with a desired lag of six months) and year 3. In addition, the two years in between the assessment of neurocognitive function will minimize practice learning and thus allow a more direct assessment of the impact of kidney disease on neurocognitive development. Finally, the growth component of the study will be conducted at the same time as the neurocognitive component.

In summary, three features of the proposed contact pattern merit emphasis: (i) the GFR measurement in the first two years will provide a measure of GFR change early in the study and it will serve as a good baseline measurement for the long-term change of

GFR; (ii) the availability of concurrent data on GFR and serum creatinine will provide data to develop an internally valid formula which will, in turn, provide the means to complete GFR data by estimating GFR in the odd years; and (iii) both level and changes in GFR will temporally proceed the measurement of the markers of neurocognitive function, cardiovascular risk factors and growth failure.

Table 5.4.1b depicts the samples to be collected on children enrolled in CKiD and stored at the repositories. Blood and urine samples will be collected at the second baseline visit (V1b) and at every annual visit. Nail clippings and hair samples will be collected at the second baseline visit (V1b). If the nail clippings and hair samples are not collected at V1b, then the samples will be collected and shipped at the next study visit. At Visit 4 (V4), toenail clippings will be collected and shipped to the repository. Similarly to hair and nail clippings collected at V1b, if the toenail clippings are not collected at V4, then the sample will be collected and shipped at a future study visit. The biological specimens will be stored at Fisher BioServices Corporation, the NIDDK Biosample Repository in Rockville, MD. The blood samples for storage for the genetic repository will be collected at the second baseline visit. The genetic repository, at Rutgers, the State University of New Jersey in Brunswick, NJ, will receive blood samples and process them to create immortalized cell lines and DNA samples. If inadequate samples are collected at V1b, then additional whole blood will be collected and shipped to the Genetic Repository (Rutgers) at V3 or a future study visit.

Table 5.4.1b Repository Samples with Time-on-Study as Time Scale

Variable	Year						
	0	1		2	3	4/6/8/ 10/12/14	5/7/9/ 11/13/15
	Pre-V	V1a	V1b	V2	V3	V4/V6/V8/ V10/V12/V14	V5/V7/V9/ V11/V13/V15
Blood Samples[a]			X	X	X	X	X
Urine Samples			X	X	X	X	X
Nail Clippings[b,c]			X			X	
Hair Samples[b]			X				
Genetic Specimen[d,e]			X				

[a] Serum and Plasma will be collected and shipped to the Biosample Repository.

[b] Nail clippings and hair samples not collected at V1b will be collected and shipped to the Biosample Repository at the next study visit.

[c] At V4, toenail clippings will be collected and shipped to the Biosample Repository. If sample is not collected at V4, then the sample will be collected at a future study visit.

[d] Whole blood will be collected and shipped to Genetic Repository.

[e] If inadequate samples of whole blood are collected at V1b, additional whole blood will be collected and shipped to the Genetic Repository (Rutgers) at V3 or a future study visit.

5.4.2 Irregular Study Visits (previously referred to as Accelerated Study Visits)

The CKiD protocol includes irregular study visits for children with a high probability of reaching ESRD within the calendar year following a study visit, children who are scheduled for renal replacement therapy before their next study visit or children who are moving outside of the CKiD area, transitioning to adult care or other long-term factors which prevent the participant from returning to a participating CKiD site. The rationale for irregular study visits in these children is to attempt to capture the clinically relevant changes in exposures at low levels of GFR, but before the onset of renal replacement therapy and to obtain clinically relevant data on a population who will be unable to complete regular study visits at participating sites.

These children will have their next study visit accelerated from 12 months in the future to within 3 months of the scheduled renal replacement therapy initiation. Irregular study visits will consist of the collection of cardiac MRI data (if applicable) and the next consecutive study visit (i.e., a CVD visit or a NC/Growth visit). Iohexol GFR data will not be collected. Also, if the cardiac MRI data cannot be obtained during the scheduled irregular visit, the measurements should be obtained prior to initiation of RRT. Furthermore, in instances when the next consecutive visit is a NC/Growth visit, the child will receive a modified NC. Also, laboratory values collected during the irregular visit will be used to calculate an estimated GFR.

For children requiring an irregular study visit, the irregular visit will be a CKiD study visit prior to beginning the Post Renal Replacement Therapy or Continued Follow-up protocol. In the event that the renal replacement therapy is not initiated or other reasons specified above (i.e., transition to adult care) do not happen after the irregular visit has occurred, then the participant will return to completing regular CKiD study visits.

5.4.3 Continued Follow-up Protocol

Participants will be given the option to participate in the continued follow-up protocol after they have renal replacement therapy, pregnancy, unable to reach or withdrawal (i.e., lost to regular follow-up). However, children who have a cancer diagnosis will be ineligible to participate in the follow-up protocol. The follow-up protocol will be composed of two components: an interview/survey and chart review. For convenience, the follow-up interview/survey will be completed via phone, in-person interview, mail or on-line. During the interview/survey, renal therapy status data will be obtained. Additional data such as sociodemographic information, medical history, health care utilization status, medication use, physical symptoms and quality of life data may also be collected. In conjunction with the follow-up interview/survey, the coordinator will collect data (i.e., lab results) from chart review to ascertain accurate data and the data may be reviewed by a researcher selected by the CKiD study who is not affiliated with the clinical site. Ideally, the follow-up protocol should be scheduled to occur annually based on the anniversary date of the participant's baseline (V1a) visit (± two months). However, for participants who disenrolled prior to the addition of the follow-up protocol, their first follow-up will be completed as soon as possible and the subsequent follow-up interviews/surveys will occur annually based on the anniversary baseline (V1a) date (± two months).

5.4.4 Post Renal Replacement Therapy (RRT) Protocol for Dialysis and Transplant Participants

At selected sites, participants will be invited to participate in the renal replacement therapy protocol after they begin regular dialysis treatment or have a kidney transplant (i.e., RRT event date). The post RRT visits will be similar but not identical for transplanted and dialyzed participants who initiate therapy after the RRT protocol is implemented.

For transplanted participants, the first baseline visit (TV1a) will consist of the collection of iohexol GFR, cystatin C, serum creatinine and proteinuria data. At the second baseline visit (TV1b), transplanted participants will complete the BRIEF and NIH tool box tests. At the subsequent even visits, extensive cardiovascular measurements (i.e. ABPM, ECHO, cIMT, cMRI and vascular tests), BRIEF and specific TV1a visit data will be collected. The subsequent odd visits for the transplanted participants will be a combination of their specific TV1a and TV1b visits (see Table 5.4.4a).

For dialyzed participants, the first baseline visit (DV1a) will consist of a 24 hour urine collection to calculate residual urine volume, Kt/V measurements and NIH Toolbox test data. However, if the NIH toolbox was completed within 6 months prior to the initiation of dialysis, it should not be completed at the D1a visit. The second baseline visit (DV1b) will include the collection of extensive cardiovascular measurements (i.e., ABPM, ECHO, cIMT, cMRI, vascular tests). The subsequent even visits will include NIH Toolbox and cardiovascular data collection but no cMRI and vascular test data. The subsequent odd visits for dialyzed participants will be parallel to the second baseline visit (DV1b) with the addition of some laboratory markers (see Table 5.4.4b).

5.4.4.1 Post RRT Protocol Visit Schedule

The RRT event date (i.e., anniversary date) will be used to project the visit dates. Although scheduling study visits will be based on the participant's availability, it is expected that the visits will be scheduled as follows:

- The first baseline visit will be scheduled within one month of the RRT event. However, if the visit is difficult to schedule, the visit should occur within 3 months of the RRT event date.
- The second baseline visit will be scheduled 6 months (± 3 months) after the RRT event date. For visits that are difficult to schedule, the second baseline visit should not occur no more than 9 months after RRT event date.
- Pending funding for an additional five years, participants will be scheduled to return annually for subsequent post RRT visits. The post RRT V2 will be scheduled 12 months after the RRT event date. For visits that are difficult to schedule, post RRT V2 should not occur no more than 18 months after RRT event date. The subsequent post RRT visits will be scheduled annually (± 6 months) based on the anniversary date of the RRT event. Specifically, these visits should be scheduled between certain time periods:
    - Post-RRT V3 should occur between 19 to 30 months after the RRT event date.
    - Post-RRT V4 should occur between 31 to 42 months after the RRT event date.

- Post-RRT V5 should occur between 43 to 54 months after the RRT event date.
- Dialyzed participants can be treated by peritoneal or hemodialysis. For participants receiving hemodialysis treatment, the ECHO and cMRI) should be scheduled the day after dialysis treatment. For participants receiving peritoneal treatment, there are no scheduling restrictions.

If any of the test procedures and/or measurements (e.g., ECHO, ABPM, vascular testing, cardiac MRI, neurocognitive tests etc.) are not obtained during the participant's scheduled visit, they should be completed within three months of the originally scheduled visit.

5.4.4.2 Participants who have Multiple RRT Events

In the event that a participant experiences a subsequent RRT (i.e., has a kidney transplant after dialysis initiation or initiates dialysis after a kidney transplant), the visit schedule and anniversary date will be based on the new RRT event.

5.4.4.3 Contact Pattern for Participants who have RRT after Protocol Amendment 2017

Tables 5.4.4a and 5.4.4b depicts the contact pattern and the corresponding data to be obtained for transplanted and dialyzed participants.

5.4.4.4 Contact Pattern for Participants who had RRT prior to Protocol Amendment 2017

For participants who initiated RRT prior to the instauration of the RRT protocol (i.e., prevalent cohort), their first post RRT follow-up visit will be completed as soon as possible. The specific post RRT visit number will be determined based on the length of time (months/years) since their most recent RRT event occurred. Also, the measurements performed will be determined based on the contact pattern illustrated in Tables 5.4.4a and 5.4.4b with the exception that ioheoxol GFR data will be collected for transplanted participants' at their first post RRT visit. Thereafter, the subsequent follow-up visits will occur annually based on the anniversary RRT event date.

(Colors illustrate the differences between the Post-Transplant and Post-Dialysis Protocols)

Table 5.4.4a. Measurements for Post-Transplant Protocol

Topic	Variable	Months post-Transplant			
		1	6	12 / 36	24 / 48
		TV1a	TV1b	TV2 /T V4 Even visits	TV3/TV5 Odd visits
	Family Information	♦	♦	♦	♦
Kidney	Iohexol-based GFR	X		X	
	Cystatin C	X		X	X
	Serum Creatinine	X		X	X
	Central Urine Creatinine and Protein	X		X	X
	Local Urine Creatinine and Urine Protein	X		X	X
	Central Renal Panel	X		X	X
	Central Uric Acid	X		X	X
	Local Complete Blood Count	X		X	X
	Local Pregnancy Tests	X		X	X
	Local Renal Panel	X		X	X
Cardiovascular	Clinical Blood Pressure (centrally calibrated)	■	■	■	■
	Clinical Blood Pressure (locally measured)	■	■	■	■
	Lipid Profile			■	
	Ambulatory Blood Pressure Monitoring			■	
	Echocardiography			■	
	Carotid Intima-Media Thickness[a]			■	
	Cardiac MRI[b]			■	
	Vascular Tests[c]			■	
Neurocognitive	BRIEF		▲	▲	▲
	NIH Toolbox Cognition Tests[d]		▲		▲
	NIH Toolbox Emotion Tests[d]		▲		▲
Growth	Height/Length and Weight	●	●	●	●
	Head Circumference[e]	●	●	●	●
	Mid-Arm Circumference[f]	●	●	●	●
	Waist and Hip Circumferences[g]	●	●	●	●
	Tanner Stage	●		●	●
	Physical Activity Monitoring[h]		●	●	●
	Intact Parathyroid Hormone (iPTH)		●		●
	High Sensitivity CRP (hsCRP)		●		●
	Grip Strength[i]		●		●
Repository/Stored	Biological samples		X	X	X
	Genetic samples		X		

[a] **Carotid IMT**: At selected sites, sub-set of participants who are 5 years old and older will have carotid IMT performed.
[b] **Cardiac MRI**: At selected sites, sub-set of participants who are 8 years old and older will have cardiac MRI performed.
[c] **Vascular Tests**: At selected sites, sub-set of participants who are 5 years old and older will have vascular tests performed.
[d] **NIH Toolbox Tests**: At selected sites, sub-set of Cohort participants who are 3 years old and older will complete NIH toolbox texts.
[e] **Head Circumference**: Head circumference will be measured at every study visit for children 3 years old and younger.
[f] **Mid-Arm Circumference**: Mid-arm circumference will be measured at every study visit for the entire cohort.
[g] **Waist and Hip Circumferences**: Waist and Hip circumference will be measured at every study visit for the entire cohort.
[h] **Physical Activity Monitor**: At selected sites, sub-set of the entire cohort will have physical activity monitoring.
[i] **Grip Strengh**: Grip strength will be measured in participants 6 years old and older.

Table 5.4.4b. Measurements for Post-Dialysis Protocol

Topic	Variable	Months post-Dialysis			
		1	6	12 / 36	24 / 48
		DV1a	DV1b	DV2 / DV4 Even visits	DV3/DV5 Odd visits
	Family Information	♦	♦	♦	♦
Kidney	24 hour Urine Collection (PD Only)	X		X	X
	Central Renal Panel	X		X	X
	Central Uric Acid	X		X	X
	Local Kt/V	X		X	X
	Local Complete Blood Count	X		X	X
	Local Pregnancy Tests	X		X	X
	Local Renal Panel	X		X	X
Cardiovascular	Clinical Blood Pressure (centrally calibrated)	■	■	■	■
	Clinical Blood Pressure (locally measured)	■	■	■	■
	Lipid Profile			■	
	Ambulatory Blood Pressure Monitoring		■	■	■
	Echocardiography		■	■	■
	Carotid Intima-Media Thickness[a]		■	■	■
	Cardiac MRI[b]		■		■
	Vascular Tests[c]		■		■
Neurocognitive	BRIEF		▲	▲	▲
	NIH Toolbox Cognition Tests[d]	▲		▲	
	NIH Toolbox Emotion Tests[d]	▲		▲	
Growth	Height/Length and Weight	●	●	●	●
	Head Circumference[e]	●	●	●	●
	Mid-Arm Circumference[f]	●	●	●	●
	Waist and Hip Circumferences[g]	●	●	●	●
	Tanner Stage	●		●	●
	Physical Activity Monitoring[h]		●	●	●
	Intact Parathyroid Hormone (iPTH)		●		●
	High Sensitivity CRP (hsCRP)		●		●
	Grip Strength[i]		●		●
Repository/Stored	Biological samples		X	X	X
	Genetic samples		X		

[a] **Carotid IMT**: At selected sites, sub-set of participants who are 5 years old and older will have carotid IMT performed.
[b] **Cardiac MRI**: At selected sites, sub-set of participants who are 8 years old and older will have cardiac MRI performed.
[c] **Vascular Tests**: At selected sites, sub-set of participants who are 5 years old and older will have vascular tests performed.
[d] **NIH Toolbox Tests**: At selected sites, sub-set of Cohort participants who are 3 years old and older will complete NIH toolbox texts.
[e] **Head Circumference**: Head circumference will be measured at every study visit for children 3 years old and younger.
[f] **Mid-Arm Circumference**: Mid-arm circumference will be measured at every study visit for the entire cohort.
[g] **Waist and Hip Circumferences**: Waist and Hip circumference will be measured at every study visit for the entire cohort.
[h] **Physical Activity Monitor**: At selected sites, sub-set of the entire cohort will have physical activity monitoring.
[i] **Grip Strengh**: Grip strength will be measured in participants 6 years old and older.

6. STUDY DATA

The progression of CKD results from a complex process of adaptive physiologic, molecular, and biochemical changes after loss of functional renal mass. Socioeconomic, nutritional and genetic factors may affect rates of progression in patients with similar diseases and in patients with different ethnic origin. Extensive data on each of these factors will be systematically collected over the course of the CKiD study to assess the relative contribution to progression, and the effects of kidney disease progression on a variety of outcomes. Data collection forms will be available in English and Spanish. Data to be collected are described in detail in the following sections: 6.1 sociodemographic, comorbidity, anthropometric, psychosocial and health care utilization measures; 6.2 kidney function measures; 6.3 neurocognitive measures; 6.4 cardiovascular measures; and 6.5 growth measures. Identification of predisposing genetic factors and novel biomarkers of progression in stored blood and urine samples will be studied pending ancillary funding described in section 7.

6.1 Comorbidity, Psychosocial and Health Care Utilization

Data on existing comorbidities and treatments, quality of life and health care utilization measures will be obtained by a combination of targeted physical examination, questionnaires, and structured interviews at baseline and annual follow-up visits.

6.1.1 Targeted Physical Exam

6.1.1.1 Hypertension: Standard clinic blood pressure (CBP) will be measured by a trained and certified individual at all visits using an aneroid sphygmomanometer as outlined in cardiovascular section 6.4.1.1.

6.1.1.2 Physical Growth and Development: Growth will be assessed using a combination of clinical evaluation, measurement of estimated body composition and biochemical markers. Height and weight will be recorded at all visits in order to calculate measures such as body mass index (kg/m^2). Pubertal status will be determined by physical examination and classified by Tanner stage at baseline and annual follow-up visits**.** Specifically, tanner staging will be performed at the first component of the baseline visit (V1a) and not repeated at the second baseline component (V1b). Head circumference for children 3 years old and younger, and mid arm circumference will be recorded at all visits. Also, waist and hip circumference will be recorded at all visits except for children 12 months of age and/or younger who are unable to stand. Other anthropometric measures including skin-fold thickness were considered, and rejected due to a lack of standardization and demonstrated measurement variability in other prospective longitudinal studies.

6.1.2 General History Information

6.1.2.1 Sociodemographic information: We will collect dates of birth, gender, detailed race and ethnicity of the child, parents and grandparents. In addition, parental education, occupation, census block group data and household income data will be collected. These data will be collected by parent/guardian questionnaire using standard instruments at the baseline visit. As of the June 2014 amendment, the study discontinued collecting census block group data.

6.1.2.2 Birth and Family History: Birth weight and length, gestational age, and complications during pregnancy and in the neonatal period will be collected by parent/guardian questionnaire. Parents will be asked to bring information about the child‘s birth (i.e., birth weight and length at birth) to the baseline visit. Family health and illness information of biological parents, aunts, uncles, siblings and grandparents will be collected by a structured interview.

6.1.3 Medical History Information

6.1.3.1 Kidney Disease History: Detailed information on the subjects’ underlying kidney disease and other disease comorbidity will be obtained from parent/guardian interview and by chart review in a standardized fashion at the time of the eligibility or baseline visit.

A medical chart review will obtain documentation of the underlying diagnosis of kidney disease from clinical history, pathologic (biopsy) diagnosis, kidney/bladder ultrasound and other renal imaging studies. The chart review will also obtain documentation of diagnosis of other diseases (i.e., lung, genitourinary and infectious disease). We will also collect information on history of surgical interventions and urologic surgeries, including their type and timing.

Information on age at diagnosis of kidney or urologic disease, age at onset and estimated GFR at diagnosis will be collected from structured parent/guardian interview and chart review.

6.1.3.2 Health Care Utilization: Health care resource utilization data will be collected using questionnaires and data obtained directly from CKiD subjects via annual in-person interviews.

6.1.4 Physical Symptoms: Information on kidney disease-related symptoms will be collected from structured subject and parent interviews. Children between the ages of 8 and 16, and parents/guardians of children under the age of 8, will be interviewed to obtain symptoms data. Questions about the quality and quantity of sleep will also be included in the symptoms questionnaire.

6.1.5 Assessment of Dietary Intake: Information on any herbal remedies, health supplements and/or vitamins will also be collected from structured interview at annual visits.

6.1.6 Environmental Exposures

6.1.6.1 Medication Inventory: Questionnaire will elicit information regarding environmental exposures (e.g., smoking, alcohol, medications). Medication use (prescriptions and over-the-counter) as well as use of nutritional aids, alternative medicines and time of use on day of visit will be assessed by questionnaires for all subjects at each visit. Parents/guardians will be asked to bring all medications taken by the child to the baseline and annual visits. Medications prescribed will also be obtained by annual chart review. Specific medications of interest in terms of risk of acceleration or slowing of progression of kidney disease include analgesics, lipid lowering agents,

immunosuppressants, and antihypertensive medications, particularly angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Adherence with these prescribed measures will also be assessed. Medications for diabetes, if used, as well as phosphate binders, activated vitamin D preparations, iron and erythropoietin and growth hormone use will also be recorded. Pending ancillary funding and feasibility, exposure to heavy metals (e.g., lead, arsenic, mercury and cadmium) and body accumulation will be assessed through assay of whole blood, urine and trace metal concentrations in nail clippings and hair samples. The nail clippings and hair samples will only be collected at the second baseline visit (V1b). If the nail clippings and hair samples are not collected at V1b, then the samples will be collected and shipped at the next study visit. At Visit 4 (V4), toenail clippings will be collected and shipped to the repository. If sample is not collected at V4, the sample will be collected at a future visit.

6.1.6.2 Adolescent Questionnaire

Questionnaires will be administered to assess smoking, alcohol and drug use in participants 12 years old and older. Questions from the 2005 and 2015 versions of the Youth Risk Behavior Survey (YRBS) will be used. The YRBS is a self-report instrument designed to monitor categories of priority health risk behaviors among youth.

6.1.7 Physical Activity

For participants 12 years old and older, physical activity will be determined by the use of physical activity questions from the 2005 and 2015 versions of the Youth Risk Behavior Survey (YRBS). Physical activity questions adapted from the National Health and Nutrition Examination Survey (NHANES) will be collected for all participants 2 years and older.

6.1.8 Health Literacy and Numeracy

The Short Test of Functional Health Literacy in Adults (STOFHLA), a standardized instrument, will be administered to a parent/legal guardian (i.e., caregiver) of participants and participants 15 years old or older to assess health literacy and numeracy. In the event that the participant, who is 15 years old or older, attends the visit unaccompanied by their caregiver, the participant will complete the assessment. Since the health literacy assessment is administered at one visit, it will not be administered to the caregiver at a follow-up visit. For Cohort 1, the survey will be administered at the participant's upcoming follow-up visit; however, for Cohorts 2 and 3 it will be administered at the baseline visit, or follow-up visit if the assessment was not completed at the baseline visit. In addition, numeracy assesses an individual's mastery of the basic symbols and processes of arithmetic.

6.2 Kidney Function Measures

Measurement of progression of kidney disease is substantially more difficult than diagnosis of the presence of kidney disease since progression of many forms of kidney disease is slow. Therefore, precise measurement of kidney function is crucial to the success of the CKiD study. Therefore, if collected blood is grossly hemolyzed, additional blood may be collected during the study visit.

6.2.1 Core Tests

The core tests to measure kidney function and risk of progressive decline are:

- GFR – iohexol Plasma Disappearance
- Serum Creatinine (central laboratory, local laboratory creatinine)
- Estimated GFR (Schwartz formula)
- Cystatin C
- Beta-Trace Protein
- Uric Acid
- Proteinuria (1st morning urine protein to creatinine ratio)
- Urine Creatinine
- Albuminuria (1st morning urine albumin to creatinine ratio)

The core biochemical measures are:

- Basic Metabolic Panel
- Complete Blood Count (CBC)
- Serum Albumin
- Calcium
- Phosphate
- Parathyroid Hormone (intact)
- Glucose

6.2.1.1 GFR - Iohexol Plasma Disappearance

Glomerular filtration rate (GFR) is the best known measure of kidney function. GFR represents the volume of plasma filtered each minute through the glomeruli of both kidneys. GFR is operationally defined as the clearance of a filtration marker from the plasma by the kidneys. Urinary clearance of inulin has been considered the gold standard measure of GFR; however, this requires an intravenous priming dose of inulin followed by a constant infusion to establish a steady-state inulin plasma concentration [Arant, Jr. 1972]. After equilibration, serial urine samples are collected every 10 to 20 minutes through an indwelling bladder catheter or urine collections obtained every 20 to 30 minutes. Urine flow is maintained high by providing an initial oral fluid load of 500-800 ml water per m^2 and replacing with water ml-per-ml [Dalton 1999].

In children with potential kidney disease, the use of inulin clearances is limited by several problems. First, some children may not be toilet trained and would thus be unable to provide accurate collections of timed urine. Second, urological problems are common causes of chronic kidney disease in infants and young children [USRDS 2002], and many such children will have significant vesicoureteral reflux, neurogenic bladders, and bladder dyssynergias. Collecting timed urines in such patients will be problematic

and fraught with error. Since many parents will refuse bladder catheterization for their children, the studies performed in such children are likely to be inaccurate. Third, there are technical difficulties encountered in performing inulin infusions, reaching a steady state of inulin distribution, and measuring inulin concentrations in plasma. In addition, the inulin assay is not very specific and is potentially hazardous (boiling acid reagents). These problems have rendered the standard inulin clearance to be impractical in children.

Because of the difficulties with administering and measuring inulin in children, standard endogenous creatinine clearances have been used to estimate GFR. However, it is well known that Creatinine is secreted, so that C_{Cr} exceeds C_{In}, particularly at low levels of GFR [Arant, Jr. 1972]. Exogenous tracers, such as ^{125}I-iothalamate, ^{51}Cr-EDTA, and ^{99m}Tc-DTPA yield clearance values exceeding those derived from standard inulin clearances due to renal tubular secretion [Rahn 1999, Silkalns 1973]. Moreover, despite the low dose of radioactivity in the tracers, it is unlikely that most families would approve of using repeated doses of radioactivity in their children for monitoring the progression of chronic kidney disease.

A reliable alternative to inulin clearance avoids both the use of radioactivity and continuous infusion of the marker. iohexol, a non-ionic, low osmolar, X-ray contrast medium (Omnipaque^{R}) that is safe and non-toxic and used for angiographic and urographic procedures, is eliminated from plasma exclusively by glomerular filtration [Back 1988]. Iohexol has a molecular weight of 821 daltons, a plasma elimination half-time of ~90 min, is distributed into the extracellular space and has less than 2% plasma protein binding [Back 1988, Krutzen 1984]. Iohexol is excreted completely unmetabolized in the urine with 100% recovery within 24 hours after infusion [Olsson 1983]. Since iohexol can be quantified in small samples, capillary, as well as venous, sampling can be employed [Krutzen 1990]. Extrarenal elimination of iohexol in a setting of reduced GFR is negligible [Nilsson-Ehle 1994]. Iohexol is measured in deproteinized plasma or serum. The commercially available preparations contain two isomers of iohexol, both of which are handled similarly by the body [Gaspari 1995, Krutzen 1990]. In practice the major peak, eluting at about 5 min, is used for clearance calculations [Gaspari 1995]. Most studies indicate close agreement between GFR (measured by inulin clearance) and clearance of iohexol, measured as standard urinary clearance, total body clearance, or plasma disappearance [Brown 1991,Erley 2001,Gaspari 1995,Olsson 1983,Rahn 1999].

Modeling of plasma disappearance of iohexol indicates that its excretion conforms to a two compartment open system [Gaspari 1995, Olsson 1983]. Excellent agreement with multiple sampling points has been obtained using a two-point iohexol plasma disappearance curve [Brown 1991, Gaspari 1995, Krutzen 1990]. CKiD initiated a pilot study to determine the optimal timing of testing for an accurate and reproducible determination of GFR measured by iohexol plasma disappearance for children with CKD. The clearance of iohexol (GFR) is calculated from the final slope of the plasma disappearance curve (one-compartment system approximation beginning 120 min after infusion) according to the method of Brochner-Mortenson [Brochner-Mortensen 1972]. The formula is: GFR = (0.990778 C_1) – (0.001218 C_1)^2 [Bland 1986], where C_1 =

injected amount of iohexol x slope of monoexponential line described by the two sample points/serum iodine concentration in mg/ml back-extrapolated to time zero. We validated this formula and confirmed the two most appropriate time points selected from the pilot study of 10 point disappearance of iohexol. We used a two point iohexol plasma disappearance to measure the slow component of GFR. The pilot study data also served to determine whether we needed to also measure the plasma concentration of iohexol at 10 minutes or whether the fast component of GFR can be estimated from the slow component of GFR. GFR will be expressed per 1.73m^2 of body surface area.

Single infusion of iohexol clearance to measure GFR: Children will be allowed free access to water, juice and a diet during the study. They will be examined while on current medication including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers. Ideally, two polyethylene catheters will be inserted into antecubital veins (or any acceptable vascular access can be used), one for infusing iohexol and one for drawing blood. In children where placement of two catheters is difficult, the iohexol can be delivered by a butterfly needle. A zero time blood sample is collected for serum creatinine that will be measured at the Central Laboratory by Autoanalyzer for comparison with that measured at the local lab. The complete 5.0 mL dosage of iohexol (Omnipaque 300, corresponding to 647 mg iohexol per mL) will be administered intravenously x 1 over 1 to 2 minutes followed by 10 ml of saline solution. The weight of the syringe must be obtained pre and post iohexol infusion using the same scale.

In Cohort 1, a four sample plasma disappearance was performed at 10, 30, 120 and 300 minutes. Initially, the four time points were determined based upon the results of the pilot study. Subsequently, the DCC has compared calculated GFRs using 4 time points (GFR4; concentrations at 10, 30, 120 and 300) to calculated GFRs using 2 time points (GFR2; concentrations at 120 and 300). Specifically, for the calculation of GFR2, the concentrations collected at 10 and 30 were disregarded and only the concentrations at 120 and 300 were used to calculate the slowGFR (= (infusion / area under the slow curve)x(1.73/bsa)). Using the CKiD equivalent to the Brochner-Mortesen equation, the GFR2 is calculated as 1.00959xslowGFR-0.00139xslowGFR^2. The excellent agreement (r= 1) of iGFR based on 4 points with iGFR2 based on 2 points provided support for simplifying the iohexol protocol. Therefore the study was simplified to 3 points (120, 240, 300). The simplification to 3 points enabled investigators to further compare the estimation of GFR using 3 points with 120&300 minutes and with 120&240 minutes data points. Again, the agreement was excellent between GFR based on 3 points with GFR based on 2 points (120,300). Therefore, as of the November 2010 amendment, the number of blood draws was reduced to 2 time points (120 and 300).

Using Cohort 1 and Cohort 2 iGFR measurements, investigators further examined simplifying the iohexol-based GFR component. For Cohorts 1 and 2, investigators concluded that sufficient iohexol-based GFRs have been measured to validate estimating equations across age and level of GFR except in those with higher levels of GFR [Schwartz 2012]. Available equations currently underestimates high values of iGFR, therefore to refine the estimating equation, continued measures of iohexol-based GFR are needed in participants with higher levels of GFR (i.e. GFR>90 ml/min|1.73m^2).

Therefore, iohexol-based GFR component will be continued in a sub-group of Cohort 1 and 2 participants identified as those who had iohexol-based GFRs ≥ 90 ml/min|1.73m^2 at their last study visit (as of December 2015). These participants will continue with iohexol-based GFR tests until their iGFR falls below 90 ml/min|1.73m^2. In addition, iohexol-based GFR tests will be optional for Cohort 3 participants.

Processing blood collection and Make-up GFR: The blood samples can be drawn by venipuncture or by inserting a second polyethylene catheter in the opposite antecubital vein (or any acceptable vascular access can be used.) Sampling cannot be performed through the catheter in which the iohexol was infused. These samples will be sent to the central biochemistry laboratory (CBL) for processing and analysis. In the event that the iohexol procedure cannot be completed during the study visit (i.e., IV infiltration of iohexol or inability to successfully draw all blood samples for iohexol), the participant ideally should be rescheduled for a make-up GFR within 3 months. The visit should not be repeated any sooner than 48 hours after the initial study visit if iohexol was infused. The B0 (blood collected pre-iohexol infusion for CBL chemistries, serum creatinine, cystatin C and iohexol blank) and first morning urine, if collected, must be sent to the CBL for processing and analysis. During the make-up GFR visit, a B0 blank (blood collected pre-iohexol infusion) and 2 blood samples for determining the iohexol concentrations will be collected.

If the iGFR cannot be calculated based on the iohexol results, the CBL and DCC, on a case by case basis, will determine whether or not a make-up GFR visit is recommended. In the event that it is recommended, only a B0 blank (blood collected pre-iohexol infusion) and 2 blood samples for determining the iohexol concentrations will be collected and sent to the CBL for processing and analysis.

6.2.1.2 Serum Creatinine

Additional proxy measures of GFR will be obtained. Annually, serum will be sent centrally for measurement of creatinine by autoanalyzer.

6.2.1.3 Creatinine Based Estimates of GFR

6.2.1.3.1 Original Schwartz Formula

Originally, [Schwartz 1976] developed a formula to estimate GFR from the plasma Creatinine and body length, using an empirically derived constant, k. The value of k is 0.45 for males and females 12 months to 18 months [Schwartz 1984], 0.55 for males between 19 months and 13 years (before 13th birthday) and females 19 months and older [Schwartz 1976], and 0.7 for males after 13th birthday [Schwartz 1985]. This formula generally provides a good estimate of GFR (r ~ 0.9) when compared with Creatinine and inulin clearance data [Hellerstein 1998,Schwartz 1976]. However, the variation between inulin clearance and GFR estimated by Schwartz formula is about 20%-30% [Hellerstein 1998, Schwartz 1976]. Creatinine based estimates of GFR using the Schwartz formula allow for reliable detection of only substantial progression of kidney disease (>25-50% decline in GFR). We therefore used iohexol GFR and serum creatinine to derive a GFR estimating equation that is based on easily obtained demographic and biochemical data that is applicable to the entire CKiD study population.

6.2.1.3.2 Updated Schwartz Formula

The Schwartz formula devised in the mid-1970s has been found to overestimate GFR as measured by plasma disappearance of iohexol (iGFR) [Schwartz 2009]. A collaboration of KIDMAC investigators and Schwartz performed linear regression analyses to assess precision, goodness of fit, and accuracy to develop improvements in estimating GFR. Of the formulas derived, the best formula yielded 87.7% of the estimated GFR within 30% of the iGFR, and 45.6% within 10%. With height measured in cm, a bedside calculation of 0.413*(height/serum creatinine), provides an updated Schwartz formula to estimate GFR.

6.2.1.3.3 Comparisons of the iGFR and the eGFR

Comparison of the relationships between the iGFR and the eGFR (based on the formula published in Kidney International 2012 by Schwartz et al. and the updated bedside formula published in JASN 2009 by Schwartz et al.) with biomarkers of CKD severity has shown that the eGFR reproduces the same epidemiologic inferences as the iohexol GFR. The array of CKD-related biomarkers examined included proteinuria, hemoglobin, bicarbonate, potassium, phosphate, and SBP, DBP and height z-scores. In separate regression models by iGFR and eGFR, we described the effect of a 50% decline on the biomarker of interest (dependent variable). Overall, the eGFR yielded the same epidemiologic inferences as iohexol GFR, with most markers having a stronger relationship with eGFR than iGFR. Further comparisons using the updated bedside GFR [Schwartz 2009] indicated that the associations with the bedside GFR equation (bedGFR) were comparable with the iGFR, although slightly attenuated, which was expected as the bedside formula is only based on height and serum creatinine. In addition to the estimated GFR, the bedGFR will be reported for all participants.

6.2.1.4 Cystatin C

Cystatin has recently been proposed as a valuable marker of renal function, but this has not yet been validated in a large scale epidemiological study. Cystatin C is a nonglycosylated 13.3-kDa basic protein produced by all nucleated cells. The production rate is not altered by inflammatory conditions or diet. The structure of the cystatin C gene and its promoter indicate that the gene is of the house-keeping type. The low molecular mass of cystatin C in combination with the stable production rate suggests that the major determinant of serum cystatin concentration is glomerular filtration rate. During the last ten years there have been many research abstracts and published papers describing the normal levels of cystatin C and comparing cystatin C with serum creatinine as a parameter for GFR [Bökenkamp 1998, Coll 2000, Filler 1997, Fischbach 2002, Hoek 2003,Laterza 2002, Martini 2003, Newman 1995, Norlund 1997, Randers 2000, Randers 1999].

The methods of the cystatin C assay as well as the estimation of clearance in these patients have been varied. A meta-analysis comparing $P_{cyst\ C}$ with P_{Cr} as a marker for kidney function was based on articles published as of December 31, 2001, and on conference abstracts from annual meetings of the American Society of Nephrology until December 2001 [Dharnidharka 2002]. The authors concluded that the meta-analysis data showed $P_{cyst\ C}$ was superior to P_{Cr} as a marker for GFR.

However, the medical literature remains controversial as to whether $P_{cyst\ C}$ is significantly better as a parameter than P_{cr} for detection of decreased GFR [Dussol 2002]. The comparison of these two markers of renal function will not be resolved until there are studies comparing P_{Cr} and $P_{cyst\ C}$ using standard reference methods for GFR, guidelines for the assay of P_{Cr} and $P_{cyst\ C}$ and for the cystatin C calibrator. We will include each of these measures at baseline and at all annual study visits.

6.2.1.5 Uric Acid

Uric acid is a waste product that is filtered by the kidney. Most is reabsorbed in the early proximal tubule and about half is then secreted into the urine by the mid-proximal tubule. Because of later proximal tubular postsecretory reabsorption, approximately 6 to 12 percent of the filtered load is excreted in the urine. Excessive production of uric acid or insufficient rates of filtration will increase serum uric acid levels. Volume contraction stimulates urate reabsorption and also raises serum urate levels. Renal tubular disease may impair urate reabsorption and thereby decrease serum uric acid levels. Starting at Visit 4 and at all annual visits, we will measure uric acid centrally.

6.2.1.6 Proteinuria and Urine Creatinine

Recently, a variety of studies have indicated that proteinuria is an important and independent risk factor for the progression of renal disease [Besbas 1998, Bolton 2001, Brenner 2002, Misselwitz 2002, Shinohara 2002, Stenvinkel 1999]. Proteinuria has also been documented as a risk factor for progressive decline in kidney function among children with CKD [Mitsnefes 2003a, Wingen 1997]. At the baseline visit, Visit 2 and every other year thereafter, a first morning urine will be sent centrally for assessment of protein to creatinine ratio. For children who do not wear diapers, the first morning urine should be collected at home. If the first morning urine is not collected at home or if the child is a diapered child, the clinical site will obtain a spot urine. The urine collection time will be documented for all urine samples.

6.2.1.7 Albuminuria (Urine Albumin to creatinine ratio)

Using the first morning urine that is sent centrally, we will measure urinary albumin at baseline and at all annual study visits.

6.2.1.8 Basic Metabolic Panel

A basic metabolic panel, consisting of sodium, potassium, chloride, bicarbonate, BUN, creatinine and glucose, will be run centrally and locally at baseline and at all annual visits.

6.2.1.9 Complete Blood Count

With particular attention to the hemoglobin (mg/dl) and white blood cell count, the CBC will be measured locally every year. For children who have had a CBC test performed within 30 days prior to their study visit, the results of the prior CBC test can be used instead of performing another CBC during the study visit. Anemia has been shown in adult CKD to be associated with accelerated kidney disease progression, mortality, and heart disease. The white blood cell count may be a marker of inflammation.

6.2.1.10 Serum Albumin

Low serum albumin is a strong risk factor for morbidity and mortality in adults and children with CKD. Serum albumin will be measured by the central and local laboratories at baseline and at all annual visits.

6.2.1.11 Calcium, Phosphorous and Parathyroid Hormone (PTH)

The analysis of serum calcium, phosphorus and PTH in relation to the degree of renal dysfunction will promote the understanding of the impact of altered mineral metabolism on the progression of renal failure and cardiovascular complications in children. Calcium and phosphate will be measured by the central and local laboratories at baseline, Visit 2 and every other year thereafter. Intact PTH will also be measured at the baseline visit and every other year thereafter.

6.2.1.12 Glucose

In children, hyperglycemia and insulin resistance are associated with the metabolic syndrome, a cluster of risk factors strongly linked to CKD and CVD. Serum glucose will be measured centrally and locally at baseline and at all annual visits. Pending ancillary funding, we will measure fasting insulin levels to allow for an estimation of insulin resistance.

6.2.1.13 Urine Pregnancy Test

Urine pregnancy test, Human Chorionic Gonadotropin (HCG) will be assessed locally at the first baseline visit (V1a) and at annual follow-up visits for females of child-bearing potential (post menarche). Positive tests will result in the participant no longer completing regular CKiD study visits; however, participants with positive results will be given the option to participate in the continued follow-up protocol. In addition, testing will be done in accordance with local IRB requirements or investigator preference. Sites should contact local institutions and state regulations to determine how to handle positive pregnancy tests.

6.2.1.14 Surplus of Serum at CBL

In the event that there is a surplus of serum at the CBL after the centrally analyzed tests are completed and pending additional funding, the left over serum will be used to perform additional studies such as hepcidin, 1,25 vitamin D, FGF-23, beta-Trace protein and magnesium.

6.2.1.15 Tests Performed Locally

In addition to the samples sent to the Central Biochemistry Laboratory, a renal panel will be performed locally for all study participants. If lab results are needed immediately for clinical care, they should be obtained locally. Only the results for tests performed by the Central Biochemistry Laboratory will be available on NEPHRON, the data management system, located at https://statepiaps6.jhsph.edu/nephron/groups/aspproc/.

6.2.2 Non-Core Tests for Post RRT Protocol Participants

6.2.2.1 Twenty-Four Hour Urine Collection

At selected sites, a 24 hour urine collection will be obtained in peritoneal dialysis participants at post-RRT baseline and annual study visits. Urine collection should only be obtained from those participants who are toilet trained and are able to voluntarily collect the urine. No participants should be catheterized for the urine. Also, urine samples will not be collected for participants who are incontinent at night or in diapers.

6.2.2.2 Kt/V

Kt/V is a formula used to quantify hemodialysis and peritoneal dialysis treatment adequacy. At selected sites, locally calculated Kt/V values will be obtained in dialyzed participants at post-RRT baseline and annual study visits. For hemodialysis treatment participants, we will obtain Kt/V values locally calculated within the 30 days prior to the study visits. For peritoneal dialysis treatment participants, we will obtain Kt/V values (dialysis and urine) locally calculated within the 6 months prior to the study visits.

6.2.3 Outcome Measures

6.2.3.1 Primary Outcome Measures

The primary renal outcomes will be the GFR level and slope, as measured by iohexol GFR. Methods for the analysis of these outcomes as continuous variables will be implemented (see section 8). For clinically meaningful cut-off values (e.g., slope per year greater than 10 ml/min) we will use methods appropriate for the analysis of binary outcomes.

6.2.3.2 Secondary Outcome Measures

6.2.3.2.1 Onset of ESRD (start of chronic dialysis or renal transplantation) or development of GFR <15 ml/min/1.73m². This will be a time-to-event analysis. It will be important to consider GFR at entry into the cohort study by stratification or multivariate analysis.

6.2.3.2.2 “Significant loss of renal function” defined as 50% decline or 25 ml/min/1.73m² decline in GFR from baseline. This will also be a time-to-event analysis that needs to take into account baseline GFR.

6.2.3.2.3 Composite clinical outcome defined by the occurrence of either a 50% decline, or a 25 ml/min/1.73m² decline in GFR from baseline, or onset of ESRD.

6.2.3.2.4 Slope of change in proteinuria over time as assessed by a spot urine protein/urine Creatinine ratio (UP/Cr). We will also assess for new overt proteinuria – UP/Cr > 0.2 (or >4 mg/m^2/hr of proteinuria).

6.2.3.2.5 All-cause death will be captured as an end point. Although very uncommon in children with CKD, we will monitor for this outcome. “Renal specific death” is difficult to define, and would be even more unlikely in children, as few patients die directly of renal disease.

6.3 Neurocognitive Measures

CKiD will conduct a battery of neurocognitive assessments at the second baseline visit (V1b), and every two years thereafter through V7. Beginning at V9, the study will discontinue performing psychological assessments, which are administered by the site's psychologist (refer to Table 5.4.1a for visit pattern). In the event that the participant demonstrates neurocognitive deficits, problems or inefficiencies at study visit 7, the site should encourage the parents and nephrologist to have follow-up testing within the participant's school or community.

Age-specific neuropsychological tests will be administered to all study participants to measure areas of cognition, development and behavior; however, cognitive tests are only standardized in English. In addition to the battery of neurocognitive assessments, CKiD will employ a behavior coding mechanism that will provide examiner perception of the reliability of the test data collected and will assist in determining why a particular task was not administered or why the data should be marked in the data set because of its low reliability. This rating will be conducted for each task that is administered (e.g., subtests of larger batteries) and should be completed immediately after the task is completed. This coding system is included in Appendix C and involves a 2-point code for each task (e.g., 1.0 for a typical reliable administration).

6.3.1 Core Tests

Based on the availability of resources and feasibility of performing the psychological assessments, the core tests for cognitive and developmental assessment:

- Mullen Scales of Early Learning (Mullen Scales) – 6 to 29 months
- Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) – 30 months through 5 years
- Wechsler Abbreviated Scales of Intelligence Second Edition (WASI II) – 6 years and older
- Conners' Kiddie Continuous Performance Test (K-CPT) – 4 to 5 years
- Conners' Continuous Performance Test II (CPT-II) – 6 years and older
- Delis-Kaplan Executive Function System:
    - Tower Subtest (D-KEFS Tower) – 6 years and older
    - Verbal Fluency Subtest (D-KEFS Verbal) – 6 years and older
    - Figural Fluency Subtest (D-KEFS Figural) – 6 years and older
    - Color-Word Interference Subtest (D-KEFS Color-Word) – 6 years and older
- Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV) Digit Span Subtest – 6 to 16 years
- Wechlser Intelligence Scale for Children Fourth Edition Integrated (WISC-IV-I) Spatial Span Subtest – 6 to 16 years old
- Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) Digit Span Subtest (ONLY the Forward & Reverse Components) – 17 years and older
- Wechsler Memory Scale Third Edition (WMS-III) Spatial Span Subtest – 17 years and older

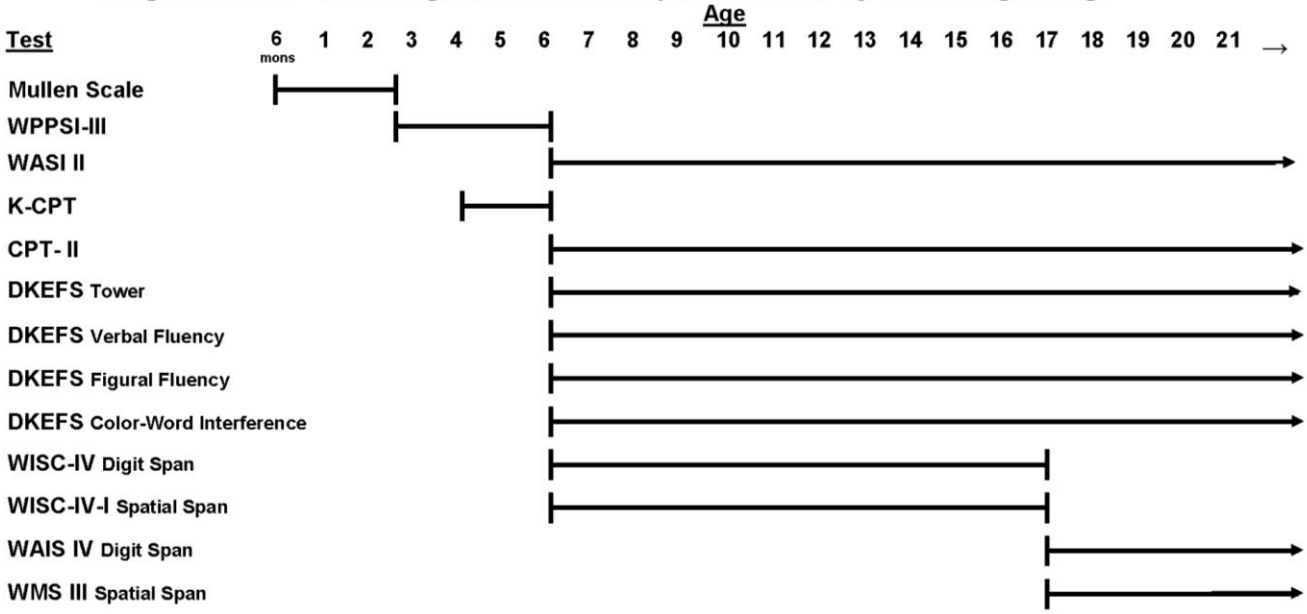
The core tests for behavioral assessment are:

- Behavior Assessment System for Children – Second Edition (BASC-2)
  - Parental Rating Scales (BASC-PRS) – 2 to 21 years
  - Self Report of Personality, College Version (BASC-SRP COL) – 21 to 25 years
- Quality of Life:
  - Pediatrics Quality of Life Scale – Parent Report (PedsQL-P) – 2 to 18 years
  - Pediatrics Quality of Life Scale – Child Report (PedsQL-C) – 8 to 17 years
  - Pediatrics Quality of Life Scale – Young Adult – 18 years and older
- Behavior Rating Inventory of Executive Function
  - Preschool Version (BRIEF-P) – 2 to 5 years
  - BRIEF – 6 to 18 years
  - Adult Version (BRIEF-A) – 18 years and older

6.3.1.1 Description of Cognitive and Developmental Assessments-Core Tests

The diagram below depicts the age ranges to which each of the tests are applicable.

Diagram 6.3.1.1 CKiD Cognitive and Developmental Tests by Chronological Age



6.3.1.1.1 Mullen Scales of Early Learning

Children aged 6 months to 29 months will be administered the Mullen Scales of Early Learning (AGS Edition). The Mullen Scales of Early Learning is a comprehensive measure of development for children, from birth to 68 months. It will be used for children up to 29 months of age. For children over the age of 29 months, the WPPSI-III (see below) will be administered to measure development and cognitive function. The test generates six age-normed scores: the Gross Motor Scale and four Cognitive Scales (Visual Reception, Fine Motor, Receptive Language, and Expressive Language). An Early Learning Composite Score is generated based on the four Cognitive Scales, and

serves as a measure of general intelligence/development. Test administration requires a test kit which includes all the necessary items and materials for use during the assessment. It takes approximately 15 minutes to complete for infants, and approximately 25 minutes for children ages 24 to 29 months [AGS 2004b].

6.3.1.1.2 Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III)
Children, aged 2.5 to 16, will receive various tests of intelligence. Specifically, children ages 2.5 through 5 years will be administered the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) to measure intelligence. Although the test is applicable for up to 7 years of age, we will administer the WASI for ages 6 and older.

The WPPSI-III is a measure of general intelligence which has been thoroughly revised to address issues of developmental sensitivity. The test will be administered in two forms: WPPSI-III 2:6-3:11 and WPPSI-III 4:0-7:3. The WPPSI-III 2:6-3:11 for children aged 2 years 6 months through 3 years 11 months, includes four core subtests: Receptive Vocabulary, Information, Block Design, and Object Assembly. The WPPSI-III 4:0-7:3, which will be administered to children aged 4 to 5 years 11 months, includes seven core subtests: Information, Vocabulary, Word Reasoning, Block Design, Matrix Reasoning, Picture Concepts, and Coding. Both configurations of the WPPSI-III generate composite scores for Verbal IQ, Performance IQ, and Full Scale IQ. Age-based standard scores are generated for all indices. The younger children should take approximately 25-35 minutes to complete the WPPSI-III, while the older children may require about 45 minutes [Harcourt 2004].

6.3.1.1.3 Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II)
Children aged 6 years and older will be administered the Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II). The WASI-II is designed as a reliable brief measure of general cognitive functioning, and consists of four subtests. CKiD will use the 2-item WASI-II that includes Vocabulary and Matrix Reasoning. The results from these subtests produce a 2-subtest IQ score. Age-based standard scores are generated for subtests and for the 2-scale IQ. This test should require approximately 35 minutes for completion [Wechsler 1999].

6.3.1.1.4 Conner's Continuous Performance Test: Kiddie Version (K-CPT)
The Conner's Continuous Performance Test: Kiddie Version (K-CPT) will be administered to all subjects aged 4 through 5 years. The K-CPT is a computer-conducted test of attention which parallels the Conner's Continuous Performance Test Second Edition (CPT-II) described below. The K-CPT takes 7 minutes to complete and generates age-based standard scores for a variety of attention processes (e.g., selective attention, sustained attention, variability, reaction time) [Conners 2003,PAR Inc. 2004].

6.3.1.1.5 Conner's Continuous Performance Test Second Edition (CPT-II)
The Conner's Continuous Performance Test Second Edition (CPT-II) will be administered to all children of ages 6 years and older. The CPT-II is used to assess visual attention, vigilance and inhibitory control/impulsivity. Administration requires approximately 15 minutes and provides age-based standard scores for key attention

measures such as number of omission and commission errors, variability, and reaction time [Conners 2004, Klecker 2003].

6.3.1.1.6 Delis-Kaplan Executive Function System Subtests
The D-KEFS consists of nine tests that comprehensively assess the key components of executive functioning. For this study, the following four (4) D-KEFS subtests, will be used and administered to all children ages 6 years and older: Tower, Verbal Fluency, Figural Fluency and Color-Word Interference. While the normative sample for the subtests actually begins at age 8 years, we will use it for 6 and 7 year olds given the longitudinal nature of many of our CKiD-II research questions. Obviously, age-based standard scores will not be generated for 6 and 7 year old age groups but, rather, raw scores will be used to address change in functioning over time. Administration of the D-KEFS subtest will require approximately 10 minutes, while each of the other three will require approximately 5 minutes each to complete. Therefore, it will take approximately 25 minutes to complete all four subtests.

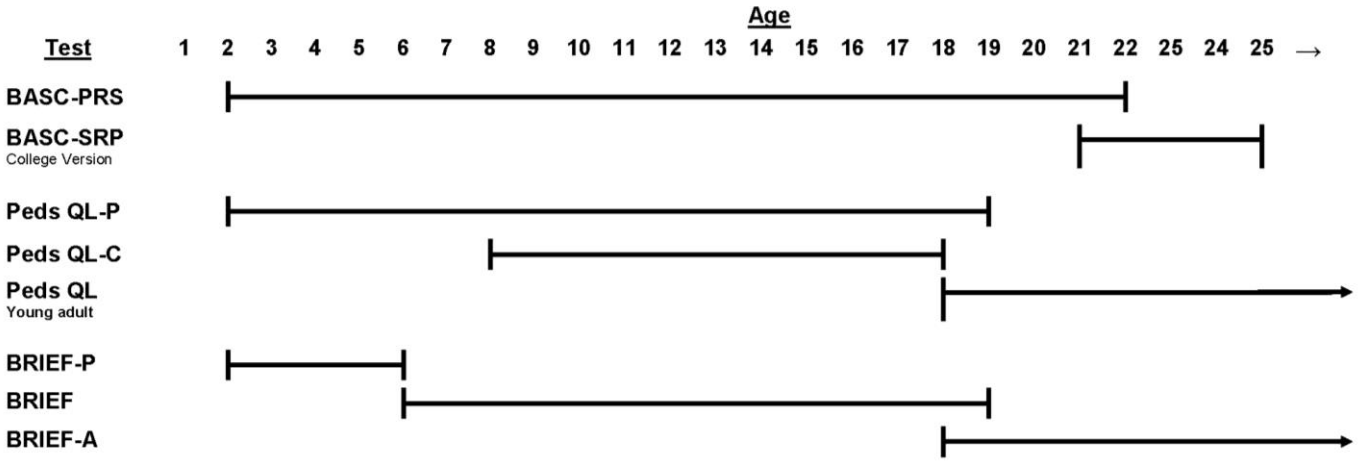
6.3.1.1.7 Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV) Digit Span Subtest and WISC-IV Integrated (WISC-IV-I) Spatial Span Subtest
The WISC-IV includes several span subtests. For this study, the Digit Span Subtest will be administered to all children ages 6 to 16 years old. One component of the WISC-IV Digit Span Subtest requires individuals to repeat a sequence of verbally-presented numbers forward, and the second component requires the individual to repeat a sequence of verbally presented number in reverse order. Age-based standard scores will be generated for the total score, forward, and reverse sequences. Like the WISC-IV Digit Span subtest, the WISC-IV-I Spatial Span subtest includes forward and backward portions of the test. Therefore, the Digit Span Forward can be compared with the Spatial Span Forward score and similarly the backward scores are comparable. Each subtest should require approximately five (5) minutes to administer.

6.3.1.1.8 Wechsler Adult Intelligence Scale Fourth Edition (WAIS IV) Digit Span Subtest
The WAIS Fourth Edition (WAIS-IV) is available for use; therefore, the WAIS-IV should be administered. Similar to the WISC-IV Digit Span Subtest, the WAIS Digit Span Subtest requires individuals to repeat verbally presented numbers in both forward and reverse order. Only the WAIS IV includes a Sequencing component and we will ONLY administer the Digits Forward and Digits Reversed sections. Therefore, a total score will not need to be generated. This subset will be administered to all children of ages 17 and older, and should require approximately five (5) minutes to administer. Age-based standard scores will be generated for the forward and reverse sequences.

6.3.1.1.9 Wechsler Memory Scale Third Edition (WMS-III) Spatial Span Subtest
The WMS Third Editions (WMS III) Spatial Span Subtest will be administered to all participants, ages 17 years old and older. Similarly to the WISC-IV-I Spatial Span Subtest, the WMS-III should require approximately five (5) minutes to administer.

6.3.1.2 Description of the Behavioral Assessments-Core Tests
The diagram below depicts the age ranges to which each of the tests are applicable.

Diagram 6.3.1.2 CKiD Behavioral Assessment Tests by Chronological Age



6.3.1.2.1 Behavior Assessment System for Children – Second Edition (BASC-2)
The Behavior Assessment System for Children – Second Edition (BASC-2) includes both parent and self-report forms. The Behavior Assessment System for Children - Parental Rating Scales (BASC-PRS) will be completed by parents of subjects aged 2 to 21 years. The Behavior Assessment System for Children – Self-Report of Personality, College Version (BASC-SRP COL) will be completed by young adult participants age 21 to 25. Each version provides an evaluation of a number of scales tapping externalizing problems (e.g., aggression, hyperactivity), internalizing problems (e.g. depression, anxiety), school problems (e.g., attention, learning), and adaptive skills (e.g., adaptability, social skills). A broad composite, the Behavioral Symptoms Index, also is generated. These scales are generally consistent across parent forms, and the normative base is quite extensive. The parent version takes 15 to 20 minutes for a literate parent to complete, and the self-report version takes 20 minutes [AGS 2004a, Reynolds 1998, Sandoval 1998].

6.3.1.2.2 Pediatric Quality of Life (PedsQL)
The Pediatric Quality of Life (PedsQL) will be completed by the parent of children aged 2 years to 18, and by children 8 years and older at all sites on a yearly basis starting at baseline. The PedsQL is a 23-item generic health status instrument. In children aged 2 to 17 years old, the instrument assesses five domains of health (Physical Functioning, Emotional Functioning, Psychosocial Functioning, Social Functioning, and School Functioning) [Varni 2001]. However, the young adult version assesses four domains (Physical Functioning, Emotional Functioning, Social Functioning, and Work/School Functioning). The inventory takes approximately 5 minutes to complete [Varni 2004].

6.3.1.2.3 Behavior Rating Inventory for Executive Functions – Preschool Version (BRIEF-P)

Parents of children aged 2 to 5 years 11 months will receive the Behavior Rating Inventory for Executive Functions – Preschool Version (BRIEF-P). The BRIEF-P is a 63-item questionnaire that assesses a child's executive functions within the context of home and preschool environments. Three clinical scales assess inhibitory self-control, flexibility and emergent metacognition. Two validity scales are also derived to measure excessive negativity and inconsistency of responses. Excellent reliability and validity have been demonstrated. It should take 15 minutes for a literate parent to complete [Gioia 2002b, Gioia 2002a, Isquith 2004].

6.3.1.2.4 Behavior Rating Inventory for Executive Functions (BRIEF)

Parents of children, ages 6 to 18 years will complete the Behavior Rating Inventory for Executive Functions (BRIEF). The BRIEF is an 86-item questionnaire that assesses executive function behaviors (i.e. inability to initiate and carry-out new and goal directed patterns of behavior). It is composed of eight clinical scales (Inhibition, Shift of Set, Emotional Control, Initiation, Working Memory, Planning, Organization, and Monitoring) and three summary scales (Behavioral Regulation, Metacognition and Global Executive Composite). The BRIEF incorporates two validity scales (measuring excess negativity and inconsistency of responses) and has shown to have excellent reliability and validity. It should take approximately 15 minutes for a literate parent to complete [Gioia 2002b, Gioia 2002a, Isquith 2004].

6.3.1.2.5 Behavior Rating Inventory for Executive Functions – Adult Version (BRIEF-A)

Participants, ages 18 and older will complete the Behavior Rating Inventory for Executive Functions – Adult Version (BRIEF-A). The BRIEF-A is a standardized measure that captures views of an adult's executive functions or self-regulation in his or her everyday environment. The BRIEF-A is based on the BRIEF and is composed of 75 items within nine nonoverlapping theoretically and empirically derived clinical scales (Inhibition, Self-Monitor, Plan/Organize, Shift, Initiate, Task Monitor, Emotional Control, Working Memory and Organization of Materials) that measure various aspects of executive functioning. It should take approximately 15 minutes for a literate participant to complete.

6.3.2 Non-Core Tests

At selected sites, we will administer new or updated version of the following assessments:

- NIH Toolbox Cognition and Emotion Batteries
- WPPSI Fourth Edition (WPPSI-IV, an updated version of WPPSI-III)
- BRIEF Second Edition (BRIEF2, an updated version of BRIEF parent form)
- BRIEF2 Self-Report (a new BRIEF form for participants 5 to 11 years old
- Ages and Stages Questionnaire-Social Emotional (ASQ-SE-2)

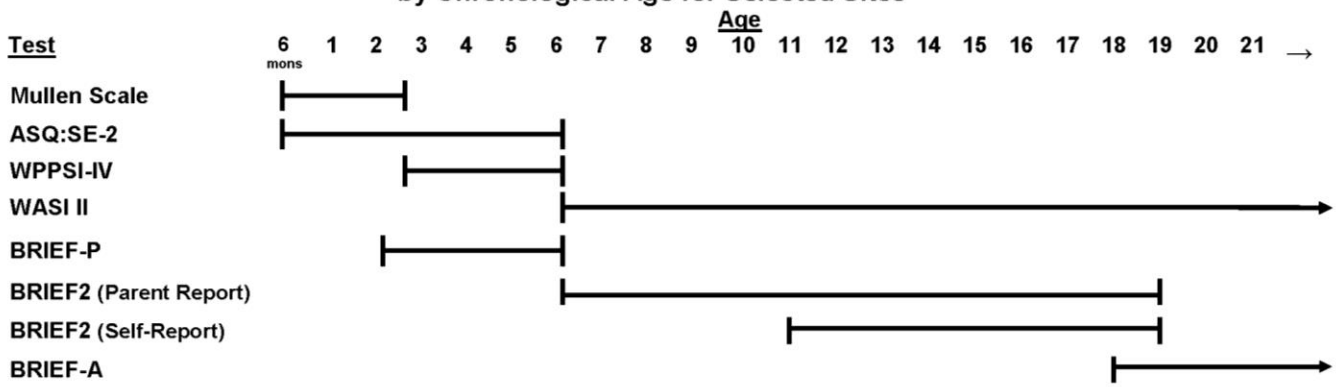
Additionally, we will continue to administer the following assessments:

- Mullen Scales of Early Learning
- WASI-II
- Parent verison of BRIEF for preschoolers (BRIEF-P)
- Young adult version of the BRIEF (BRIEF-A)

The rest of core tests for cognitive, developmental and behavioral assessment listed under section 6.3.1 will not be administered.

The diagram below depicts the age ranges to which each of the tests are applicable.

Diagram 6.3.2 CKiD Cognitive, Developmental and Behavioral Assessment Tests by Chronological Age for Selected Sites



6.3.2.1 The Age and Stages Questionnaire – Social Emotional (ASQ:SE-2)

The Age and Stages Questionnaire – Social Emotional (ASQ:SE-2) were selected to monitor very young children's social and emotional development. The ASQ:SE-2 provides an inexpensive, culturally versatile tool to identify young children at risk for social or emotional difficulties. The ASQ:SE-2 system consists of a series of 9 parent completed questionnaires that screen a child from 3 months to 71 months of age and cover 7 domains of social-emotional development: self-regulation, compliance, adaptive functioning, autonomy, affect, social-communication, and interaction with people. ASQ:SE-2 rating scales are available for ages 6, 12, 18, 24, 30, 36, 48 and 60+ months, and the targeted form will be selected based on the chronological age of the child. Total scores are produced. The ASQ:SE-2 should require a literate parent approximately 10 minutes to complete.

6.3.2.2 Wechsler Preschool and Primary Scale of Intelligence Fourth Edition (WPPSI-IV)
While the Wechsler Preschool and Primary Scale of Intelligence-III will continue to be used study-wide, at selected sites specific subtests of Wechsler Preschool and Primary Scale of Intelligence Fourth Edition (WPPSI-IV) will be administered. For children aged 2 years 6 months through 3 years 11 months, Receptive Vocabulary and Block Design subtests will be administered using the WPPSI-IV 2:6-3:11 form. For children aged 4 to 5 years 11 months, the subtests: Vocabulary and Matrix Reasoning will be administered using the WPPSI-IV 4:0-7:7 form. Age-based standard scores are generated for all indices. These subtests should require approximately 10-15 minutes to complete.

6.3.2.3 Behavior Rating of Executive Function (BRIEF)
Sites will continue to administer the parent completed Behavior Rating of Executive Function Preschool version (BRIEF-P) for children ages 2 years through 5 years, and the BRIEF-Adult (BRIEF-A) for young adults 18 years old and older. However, the BRIEF parent report that is currently administered to children 6 to 18 years old will be replaced with the updated BRIEF2 parent report. The primary modification to the BRIEF2 parent report is that the normative data was updated; however, no new items were added. The BRIEF2 parent report will continue to require a literate parent approximately 10 minutes to complete. In addition to the BRIEF-P, BRIEF-A, and BRIEF2 parent form, sites will administer a new BRIEF2 self-report form to participants who are 11 to 18 years old. The BRIEF2 self-report will also require approximately 10 minutes to complete. The BRIEF2 self-report and BRIEF2 parent report are comprised of 9 clinical scales (Inhibit, Self-Monitor, Shift, Emotional Control, Initiate [parent report only], Task Completion [self-report only], Working Memory, Plan/Organize, Task Monitor [parent report only], Organization of Materials [parent report only]) that are combined to form 3 summary scores (Behavioral Regulation Index, Emotional Regulation Index, and Cognitive Regulation Index), and 1 overall score (Global Executive Composite).

6.3.2.4

NIH Toolbox Cognition and Emotion Batteries

In general, the NIH Toolbox is a multidimensional set of brief measures assessing cognitive, emotional, motor and sensory function from ages 3 and older. At selected sites, the cognition components of the NIH Toolbox will be conducted to measure:

- Executive Function
- Attention
- Episodic Memory
- Language
- Processing Speed
- Working Memory

The following NIH Toolbox tests will be conducted for participants, age 3 – 6 to assess cognition:

- Dimensional Change Card Sort Test (DCCS)
- Flanker Inhibitory Control and Attention Test
- Picture Sequence Memory Test – 3 years and older
- Picture Vocabulary Test – 3 years and older

However, for participants who are 7 years old and older, the following NIH Toolbox tests will be conducted to assess cognition:

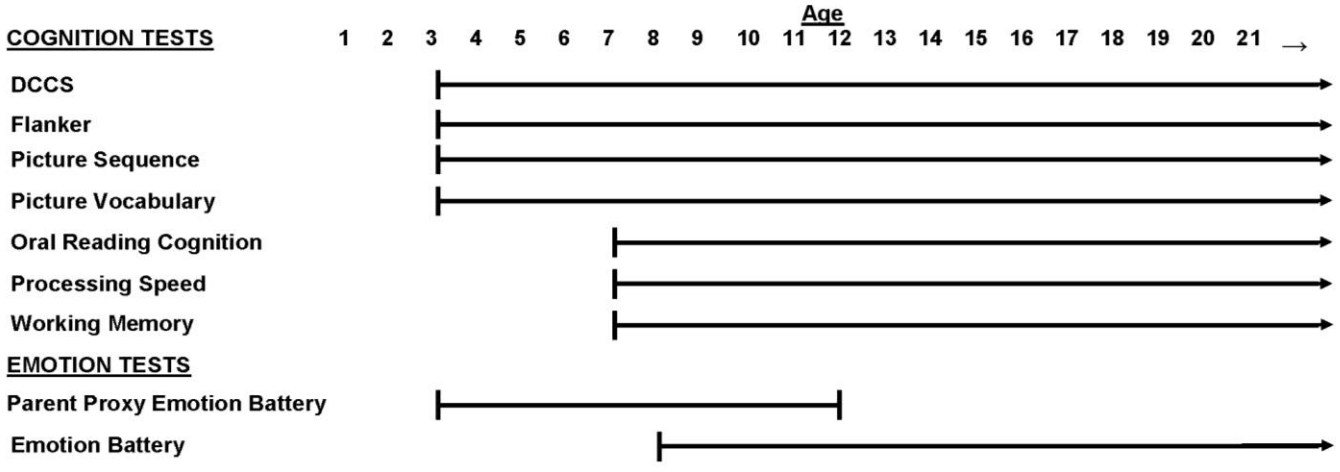
- Dimensional Change Card Sort Test (DCCS)
- Flanker Inhibitory Control and Attention Test
- Picture Sequence Memory Test – 3 years and older
- Picture Vocabulary Test – 3 years and older
- Oral Reading Recognition Tests
- Processing Speed Tests
- Working Memory Tests

Also, the following batteries will be completed to assess various measures of emotion.

- Parent Proxy Emotion Battery – parents of 3 to 12 years old
- Emotion Battery – 8 years old and older

The diagram below depicts the age ranges to which each of the tests are applicable.

Diagram 6.3.2.4 NIH Toolbox Cognition and Emotion Tests by Chronological Age



6.3.2.4.1 NIH Toolbox Dimensional Change Card Sort Test (DCCS)
Participants aged 3 and older will be administered the Dimensional Change Card Sort Test (DCCS). The DCCS is a measure of cognitive flexibility. Two target pictures will be presented that vary along two dimensions (e.g., shape and color). Participants will be asked to match a series of bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color) and then, after a number of trials, according to the other dimension (e.g., shape). “Switch” trials will be also employed, in which the participant must change the dimension being matched. For example, after 4 straight trials matching on shape, the participant may be asked to match on color on the next trial and then go back to shape, thus requiring the cognitive flexibility to quickly choose the correct stimulus. Scoring will be based on a combination of accuracy and reaction time, and the test should take approximately 4 minutes to administer.

6.3.2.4.2 NIH Toolbox Flanker Inhibitory Control and Attention Test
Participants aged 3 and older will be administered the Flanker Inhibitory Control and Attention Test. The Flanker task measures both a participant’s attention and inhibitory control. The test requires the participant to focus on a given stimulus while inhibiting attention to stimuli (fish for ages 3-7 or arrows for ages 8-85) flanking it. Sometimes the middle stimulus is pointing in the same direction as the “flankers” (congruent) and sometimes in the opposite direction (incongruent). Scoring will be based on a combination of accuracy and reaction time, and the test should take approximately 3 minutes to administer.

6.3.2.4.3 NIH Toolbox Picture Sequence Memory Test
Participants aged 3 and older will be administered the Picture Sequence Memory Test. The test is a measure developed for the assessment of episodic memory. It involves recalling increasingly lengthy series of illustrated objects and activities that are presented in a particular order on the computer screen. The participants will be asked to recall the sequence of pictures that is demonstrated over two learning trials; sequence length varies from 6-18 pictures, depending on age. Participants will be given credit for each adjacent pair of pictures (i.e., if pictures in locations 7 and 8 and placed in that order and adjacent to each other anywhere – such as slots 1 and 2 – one point is awarded) they correctly place, up to the maximum value for the sequence, which is one less than the sequence length (if there are 18 pictures in the sequence, the maximum score is 17, because that is the number of adjacent pairs of pictures that exist). The test should take approximately 7 minutes to administer.

6.3.2.4.4 NIH Toolbox Picture Vocabulary Test
Participants aged 3 and older will be administered the Picture Vocabulary Test. The Picture Vocabulary Test is a measure of receptive vocabulary and will be administered in a computerized adaptive format. The participants will be presented with an audio recording of a word and four photographic images on the computer screen and will be asked to select the picture that most closely matches the meaning of the word. This test should take approximately 4 minutes to administer.

6.3.2.4.5 NIH Toolbox Oral Reading Recognition Tests
Participants aged 7 and older will be administered the Oral Recognition. The test focuses on oral reading skill, which reflect level and quality of prior educational

experiences, and provides a fairly robust indication of verbal intelligence that is relatively undisturbed by many medical conditions that affect the brain. The participants will be asked to read and pronounce letters and words as accurately as possible. The test administrator will score the responses as right or wrong. The test will be given in a computerized adaptive format and will require approximately 3 minutes.

6.3.2.4.6 NIH Toolbox Processing Speed Tests

Participants aged 7 and older will be administered the Processing Speed Test. The test measures speed of processing by asking participants to discern whether two side-by-side pictures are the same or not. The participant's raw score will be determined based on the number of items correct in a 90-second period. The items are designed to be simple to most purely measure processing speed. This test should take approximately 3 minutes to administer.

6.3.2.4.7 NIH Toolbox Working Memory Tests

Participants aged 7 and older will be administered the Working Memory Tests. The test measures an individual's capacity to:

- process information across a series of tasks and modalities
- hold the information in a short-term buffer
- manipulate the information
- hold the products in the same short-term buffer

The participants will be presented with pictures of different foods and animals accompanied with audio recording and written text (e.g., "elephant"). The participants will then be asked to say the items back in size order from smallest to largest, first within a single dimension (either animals or foods, called 1-List) and then on 2 dimensions (foods, then animals, called 2-List). The score is equal to the number of items recalled and sequenced correctly. This test should take approximately 7 minutes to administer.

6.3.2.4.8 NIH Toolbox Parent Proxy Emotion Battery

Parents of participants aged 3 to 12 years old will complete the Parent Proxy Emotion Battery. The parent proxy emotion battery includes measures of positive affect, general life satisfaction, positive peer interaction, social withdrawal, peer rejection, empathic behaviors, self-efficacy, perceived stress, sadness and anger. For parents of children who are 3 to 7 years old, surveys to measure over anxiousness and separation anxiety will be included. The battery should take approximately 15 minutes.

6.3.2.4.9 NIH Toolbox Emotion Battery

Participants aged 8 years and older will complete the Emotion Battery. The emotion battery includes measures of positive affect, general life satisfaction, friendship, loneliness, perceived rejection, perceived hostility, self-efficacy, sadness, perceived stress, fear and anger. The battery should take approximately 12-22 minutes.

6.3.3 Outcome Measures

For the neurocognitive data, the main outcome measures will be changes in the neuropsychological test scores between baseline and every 2 years. These will be correlated with both GFR and with any change in GFR (a chronically low GFR may be associated with adverse outcome even if it has not further declined). A secondary outcome measure will be changes in the behavioral/QOL age normalized scores which will also be correlated with both GFR and with any change in GFR.

6.4 Cardiovascular Measures

The goal of this specific aim is to prospectively assess cardiac and vascular abnormalities and identify the role of traditional CVD risk factors and kidney failure risk factors for development of these abnormalities in the CKiD cohort. Symptomatic CVD is rare in these children. For the full cohort, associations between CVD disease (or disease severity) and progression (i.e., changes in GFR over time) of kidney disease will be assessed in cross sectional analyses at baseline. In addition, by repeating measures two years later in the subcohort enrolled during the first 12 month of enrollment, we will establish incident CVD disease in those disease-free at baseline, and determine rates of progression of CVD. We hypothesize that incident CVD and progression of disease will be related to CKD severity and progression. We will assess the presence of early markers of cardiomyopathy, such as left ventricular hypertrophy (LVH) and LV dysfunction, and early markers of atherosclerosis, such as increased carotid intima-media thickness (IMT) and decreased aortic compliance.

6.4.1 Core Tests

The core tests to measure cardiovascular risk factors are:

- Clinical Blood Pressure
- Ambulatory Blood Pressure Monitoring
- Echocardiography
- Serum Markers

6.4.1.1 Clinical Measurement of Blood Pressure

Hypertension (HTN) is common in children with CKD [Drukker 1991, Feld 1996, Foreman 1988, Rosenblum 1992, Solhaug 1992] but neither the relative degree of HTN nor the effect of antihypertensive medications on progressive kidney damage has been well studied. A recent report from the NAPRTCS [Mitsnefes 2003a] demonstrated that nearly half of the children enrolled in the CRI registry had HTN based upon an office BP reading obtained at time of enrollment. In that study, hypertensive children with CKD developed ESRD or decrease in GFR > 10 ml/min|1.73m^2 significantly more often after two years of follow-up than normotensive children with CKD, suggesting that HTN is indeed an important factor affecting the rate of progression of CKD in children.

Blood pressure will be measured in a standard fashion by trained, certified observers using an aneroid sphygmomanometer. Appropriately sized cuffs will be used as per the recommendations of the Working Group on High Blood Pressure in Children and Adolescents [HBP Working Group 2004]. Three BPs will be taken at 30 second intervals in the subject's right arm (unless there is a medical reason not to use it) at every study visit. While the use of auscultatory hand held units is sensitive to observer bias, several considerations were made in adopting this general approach. First, the use of a random zero device or mercury sphygmomanometer was removed from consideration due to the American Hospital Association and the Environmental Protection Agency proposals to eliminate mercury from hospitals. Secondly, electronic measurements were not selected, because these devices use an oscillometric technique. Notably, while oscillometric techniques reduce observer bias, accuracy of measurement is compromised, particularly for diastolic blood pressure, because measurements are based on proprietary algorithms of the various device manufacturers. In contrast,

aneroid devices use the auscultatory technique upon which childhood BP standards are based and that is recommended by consensus organizations [HBP Working Group 2004]. Training, certification and blood pressure monitor calibration will be scrupulously maintained.

6.4.1.2 Ambulatory Blood Pressure Monitoring (ABPM)

Ambulatory blood pressure monitoring provides multiple measurements of BP over a 24-hour period [Flynn 2002, Portman 1991, Schomig 2000] in children. ABPM allows for the creation of predictor variables such as BP load (percentage of elevated readings) and patterns of nocturnal dipping and non-dipping, which have been correlated with the development of hypertensive target organ damage.

The purpose of ABPM measurement in CKiD is to investigate the ambulatory patterns of BP in children cross-sectionally and longitudinally, and to correlate these patterns with target organ damage, such as declining GFR, proteinuria and measures of left ventricular mass index (LVMI), vascular compliance and cardiac function. The association between clinical measurement of BP and ABPM patterns will also be examined. Obtaining ABPM on the entire cohort will also allow investigators to determine the prevalence of abnormal BP patterns in children with CKD and the usefulness of monitoring as a prognostic clinical measure for progression of CKD.

Twenty-four hour ABP will be measured by protocol using a SpaceLabs™ 90217 device. CKiD investigators at the University of Texas at Houston will serve as the coordinating center for dissemination and receipt of ABPM monitors. Initializing and downloading of monitors will be done by the coordinating center or by clinical sites working with the coordinating center. Diaries will be provided with the monitors. The monitoring will be performed for 24 hours and then sent back to the ABPM center for downloading and entry into the database. For each 24-hour recording, measurements will be obtained every 20 minutes throughout the day and night at a bleed step of 8 mmHg. A diary will be kept during the monitoring to record time to sleep, time of waking, timing of any napping, and time of medication administration – particularly antihypertensive medication. Monitors will be mailed back directly from the patient to the ABPM center. Results of the monitoring will be sent to the clinical site to share with the patient. ABPM will be performed at Visit 2 and every other year thereafter. Twenty-four hour, awake and asleep mean BP and BP load; dipping status and variability will be determined. We will also compare BP's obtained by ABPM to those obtained by auscultation at the study visits. A wireless home ambulatory blood pressure cuff may be utilized for additional measurement of blood pressures at home in some children depending on funding (see Section 6.4.2.3).

We expect that children with CKD will have a high prevalence of abnormal 24 hour BP patterns. Abnormal nocturnal elevation in BP and "reverse dipping" patterns will be characterized. We hypothesize that 24-hour SBP and SBP load, and abnormal dipping will be associated with increased LVM index, carotid IMT and arterial stiffness. The prevalence of nighttime hypertension will increase with progression of renal failure. Persistent nighttime systolic hypertension may predict development and progression of studied cardiac and vascular abnormalities. In addition, it will also be associated with worsening proteinuria and accelerated progression of CKD over time. The rationale for

including the entire cohort is the importance of determining the prevalence of abnormal BP patterns in children with CKD and the usefulness of monitoring as a prognostic clinical measure for progression of CKD.

6.4.1.3 Echocardiography

Echocardiographs will be performed by standard M-mode and Doppler echocardiography. The core outcome measurements will include determination of cardiac structure, systolic and diastolic LV function, and vascular (aortic) compliance. Using cardiac and vessel parameters as dependent variables, the contribution of demographic factors, and clinical and laboratory parameters will be assessed. The decision to use M-Mode for LVM calculation is based on recommendations provided in the 4th Report on High Blood Pressure in Children and Adolescents, prepared by NHLBI's National High Blood Pressure Education Program (NHBPEP). Results from the NHBPEP (which will be published in Pediatrics, August 2004) also emphasize the use of this method as a standard procedure to calculate LVM for pediatric centers. The use of a single and relatively simple method for LVM calculation will provide the standardization among multiple participating centers.

The echocardiogram and Doppler studies will be performed in all children at Visit 2 and every four (4) years thereafter. ECHOs will be performed at individual participating sites and recorded on videotapes, but reading and data analyses of ECHO data will be performed by the Cardiovascular Core Imaging Laboratory, Cincinnati Children's Hospital Medical Center (CCHMC). Videotapes/CDs will be sent to the CCHMC with the assigned study ID number as an identifier. The reading center will not have a list of the names of participants that link to the ECHOs and ECHO reports - these will be held by the local clinical centers. Back-up tapes will be stored at the clinical sites. We anticipate that we will be able to achieve standardization and uniformity of ECHOs across sites through training, certification and pre-specified quality control monitoring. CCHMC has experience in coordinating multicenter studies including coordination of ECHOs for the industry-sponsored ramipril study, "The Effect of Ramipril on Ambulatory Blood Pressure and Left Ventricular Mass Index in Children and Adolescents with Hypertension". ECHOs will be performed by certified technicians, and standardized training and certification of designated ECHO technicians at each clinical center will be required.

However, in the event that a clinical site cannot complete the ECHO (i.e., site technician is not certified), the study visit will not be postponed. Clinical sites will proceed with the scheduled visit and collect the other study measurements (i.e., blood draw and completed forms). For clinical sites with certified technicians, Cincinnati Children's hospital will perform quality control for ECHO measurements performed by the certified technicians.

Normative data for ECHOs in children over a wide age range are available in published reports, and also are under development by the Cincinnati Children's Hospital Echo Lab, for lab-specific norms. Data for LVM index [De Simone 1992] [De Simone 1995], LV function [Mitsnefes 2004a], carotid artery [Mitsnefes 2004b] are available from publications by this group. Standardized ECHO measurements by CCHMC, including single echo lab measurements and comparison with children free of kidney disease

from the same echo lab for all cardiac and vascular parameters will provide standardization. The CKiD cohort will provide a valuable data base to establish normative data for children with CKD at multiple sites by a standard technique.

It is expected that most children in the cohort would not require sedation for the ECHO procedures. A small proportion of very young children might require sedation to facilitate the ECHO, but it was the opinion of the Cardiovascular Outcomes Subcommittee that the study could not justify applying for IRB approval of sedation in these few children because this is an elective ECHO and would not be used a part of routine clinical care. In addition, M-mode and Doppler studies proposed by CKiD require only brief patient cooperation to achieve good study quality. Hence, ECHOs will be conducted on all eligible participants without sedation.

Currently available data on echocardiographic parameters in children with CKD are from small, single-center cross-sectional studies. We will obtain ECHO measurements in the entire cohort because there is a lack of published data establishing normative findings in children with CKD. Justification for ECHO measurement in the entire cohort, the proposed time sequence and hypotheses are based on important findings reported in preliminary studies by CKiD investigators. This includes cross-sectional studies of children with CKD which report an association between severity of kidney disease and LVM index [Mitsnefes 2003c], hypertension/abnormal diurnal blood pressure pattern and LVH [Mitsnefes 2003b], LV diastolic dysfunction and LVH [Mitsnefes 2004a]. Expected findings in cross sectional analyses in CKiD are for an association between blood pressure (or a diagnosis of hypertension) and the presence of concentric LVH; those with decreased hemoglobin will have eccentric LVH. We hypothesize that LVM index will significantly correlate with SBP, and inversely correlate with hemoglobin level and GFR level. In prospective analyses, we hypothesize that changes in LVM index over time will be related to changes in SBP, hemoglobin concentration and GFR. It is expected that there will be an association between the prevalence of LV diastolic dysfunction and kidney disease severity in children with CKD. Indices of decreased LV relaxation and LV compliance (from tissue Doppler) will significantly correlate with increased LVM, high BP and increased Ca x P product/iPTH level. In children who develop LVH over time, increased LVM index will be associated with worsening of diastolic function.

To ensure adequate statistical power to determine the prevalence and progression of CV abnormalities over time, we will need to perform the CV tests on approximately 600 children in Cohort 1 who are expected to be seen at the second visit when the CVD protocol will be implemented. Based on prior work by [Johnstone 1996, Mitsnefes 2003c], we expect between 20% and 30% of the children to have prevalent CV abnormalities (specifically LVH) at baseline. Table 6.4.1.3 illustrates the statistical power for the prevalence ratio of CV abnormalities varying the size of the

Table 6.4.1.3 Detectable Prevalence Ratios for CV abnormalities among 510 children with a 2-sided alpha of 5% and power of 80%

	Percent exposed:	
Overall Prevalence:	**10%**	**30%**
20%	**1.95**	**1.66**
30%	**1.69**	**1.47**

exposed group between 10% and 30% for the 510 children in Cohort 1 who are expected to remain under follow up (i.e., the exposed group may be thought of as those 10% or 30% of children with the largest declines in GFR between the two prior CKiD study visits). We calculate the detectable prevalence ratios with a 2-sided alpha of 5% and 80% statistical power. Reading from Table 6.4.1.3, at an overall prevalence of 30%, we will have adequate statistical power to detect a prevalence ratio of 1.69 or 1.47 with 10% or 30% exposed, respectively. In addition to prevalence, we will be able to explore incidence of CV abnormalities among those children without baseline CV abnormalities during the first CKiD funding cycle, but with lower statistical power. In summary, employing the entire CKiD cohort for CV tests provides adequate statistical power to detect moderate sized effects.

6.4.1.3.1 Cardiac Structure

Left ventricular hypertrophy (LVH) and increased LVMI are well accepted measures of end organ damage and are predictive of poor patient outcome in adults with CKD [Foley 1995, Zoccali 2001]. When LVH occurs, what geometrical patterns of LVH develop, and how LVH progresses in the course of CKD in children are not known.

The following assessments will be conducted to evaluate cardiac structure in CKiD: LVM will be determined according to the American Society of Echocardiography criteria [Devereux 1977] by two-dimensional guided M-mode echocardiography. LVM index will be calculated as LVM divided by the patient's height raised to the power 2.7 ($g/m^{2.7}$) [De Simone 1992]. LVH will be defined as an LVM index greater than the sex-specific 95th percentiles for LVM index from normal children and adolescents [De Simone 1995]. LV geometry will be evaluated based on the sex-specific 95th percentiles for LVM index and relative wall thickness (value of 0.41) from normal children and adolescents [Ganau 1992]. Normal geometry is defined as LVM index and RWT below the 95th percentile. Concentric remodeling is defined as LVM index below the 95th percentile with RWT greater than the 95th percentile. Eccentric LVH is defined as LVM index greater than the 95th percentile and RWT below the 95th percentile. Concentric LVH is defined as both LVM index and RWT greater than the 95th percentile. In addition, left atrial size and volume will be determined.

6.4.1.3.2 Cardiac Function

In adults with ESRD, diastolic dysfunction of the LV is very prevalent, usually precedes systolic LV dysfunction and is associated with LVH [Fujimoto 1994]. It is not known whether children with early stages of CKD have abnormal diastolic function, what the risk factors are for decreased diastolic function or how LV function changes with progression of kidney disease.

The following assessments will be conducted to evaluate cardiac function: LV systolic performance will be assessed by shortening fraction (SF) and midwall shortening. Diastolic function will be estimated by Doppler measurements. Early diastole will be assessed using indices of LV relaxation and reported as the peak E/A wave ratio (E/A) and septal mitral annular velocities (Em), respectively. Late diastole will be determined using indices of LV compliance (E/Em ratio).

6.4.1.3.3 Vascular Compliance

Although symptomatic coronary artery disease (CAD) is not frequent in children, the atherogenic process might well begin in childhood. Abnormal aortic distensibility and stiffness determined echocardiographically have been associated with hypertension, coronary artery disease and hypercholesterolemia in adults [Dart 1991,Stefanadis 1987]. Thoracic aorta diameters will be measured and aortic strain, aortic root distensibility and aortic stiffness index will be calculated [Caro 1978].

6.4.1.4 Serum Markers

A major goal of the CKiD study is to determine risk factors for cardiovascular disease (CVD). Many known or suspected risk factors for these outcomes will be measured in blood samples.

6.4.1.4.1 General Laboratory Tests of Relevance to CVD

Proteinuria is a known marker of CVD and CKD progression [Keane 1999]. Urine protein and creatinine will be measured yearly in the entire CKiD cohort. Anemia is a known marker of CVD risk [Van der 2004]. A complete blood count will be measured yearly in the entire CKiD cohort. Calcium and Phosphorous are likely associated with vascular calcification [Davies 2001]. Serum calcium and phosphorous will be measured yearly in the entire CKiD cohort. Albumin is a key marker of nutrition and is associated with CVD and CKD outcomes. Serum albumin will be measured yearly in the entire CKiD cohort.

6.4.1.4.2 Lipids: Triglycerides (TG), HDL, LDL, VLDL

Analysis of dyslipidemia may reveal overlapping risk for the development of CVD and progression of CKD [Blacher 1999, Chavers 2002, Paoletti 2002, Stack 2002]. For example, in the Atherosclerosis Research In Communities (ARIC) study, elevated TG was a risk factor for decline in renal function within 3 years [Muntner 2000]. Total cholesterol (TC), TG, and, high density lipoprotein-cholesterol (HDL-C) will be measured on the entire cohort at Visit 2 and then every other year thereafter. Children will be instructed to fast but not thirst prior to these visits. Water or zero-calorie beverages (i.e. non-caffeinated diet drinks) and sugar free gum will be recommended. In special circumstances where fasting is difficult (i.e., long distance traveling) “clear” fluids with calories will be acceptable.

The Friedewald formula will be used to estimate low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) from the direct measurements of total cholesterol (TC), total triglyceride (TG), and high density lipoprotein cholesterol (HDL-C) [Friedewald 1972]. If the TG concentration exceeds 400 mg/dL, the formula is inaccurate and direct measurement of VLDL-C will be required to more correctly estimate LDL-C.

6.4.2 Non-Core Tests

6.4.2.1 Carotid Artery Intima-Media Thickness

Ultrasonographic measurements of carotid artery intima-media thickness (IMT) have proven to be predictive of subsequent cardiovascular and cerebrovascular events [Chambless 1997, O'Leary 1999]. IMT is an attractive tool because it provides direct assessment of sub-clinical disease and because it is noninvasive and reproducible.

In a subgroup of Cohorts 1 and 2 children enrolled in CKiD, carotid IMT will be determined by ultrasonographic measure regardless of age. However, for Cohort 3, carotid IMT will only be performed on children 5 years old and older. The sub-cohort of patients will be identified from the centers that are able to perform high frequency carotid artery ultrasound. During the developmental phase of the study, investigators surveyed the participating clinical sites and found that 8 clinical sites had the personnel and instrumentation to do the carotid IMT studies. Therefore, up to 8 clinical sites will be chosen to participate in the carotid IMT studies. Carotid artery IMT, stiffness, distensibility and other measures of vascular compliance will be determined. Carotid IMT will be related to severity and progression of kidney disease in cross sectional and prospective analyses. We hypothesize that in cross-sectional analyses, children with CKD will have higher prevalence of increased carotid IMT and decreased arterial wall compliance. We also hypothesize that IMT and carotid artery compliance will be significantly correlated with BP, GFR, high-sensitivity CRP, total cholesterol, LDL-cholesterol and Ca x P product.

6.4.2.2 Vascular Tests

To better characterize vascular function, pulse wave analysis (PWA), pulse wave velocity (PWV), and heart rate variability (HRV) will be measured using the SphygmoCor System (AtCor Medical, Sydney, Australia) [Oren 2003]. Prior to collecting these data, investigators surveyed the participating clinical sites and found that some clinical sites had the necessary personnel and instrumentation (SphygmoCor). Therefore, selected clinical sites will be chosen to participate in the Vascular Tests sub-study. For Cohort 3, the tests will only be performed on children 5 years old and older. PWA, PWV, and HRV data will be collected in conjunction with the other cardiovascular measurements.

6.4.2.2.1. Pulse wave analysis (PWA) is used to determine augmentation index (AIx), which is a measure of wave reflections that is related to adverse CV events in adults [Vlachopoulos 2010]. The recording of AIx measured with a SphygmoCor System (Atcor Medical, Sydney, Australia) will be obtained in the sitting position. A probe the size and weight of a pencil is placed on the radial artery (where the pulse is on the wrist). This device does not use needles or ultrasound or radiation. The device records the pressure waveforms with a high-fidelity micromanometer (pressure sensor) calibrated with previously obtained resting BP (SBP and DBP) [Wilkinson 1998, Wilkinson 2000, Wilkinson 2001]. A generalized transfer function validated from catheterization is used to calculate ascending aorta pressure waveforms [Wilkinson 1998, Takazawa 1996, O'Rourke 1996, Karamanoglu 1995]. Augmentation pressure (AP) is the difference between the primary outgoing wave and the reflected wave of the central arterial waveform [London 2001, Lurbe 2003]. Higher AIx indicates earlier wave reflection

increasing afterload on the heart. Reproducibility studies of PWA in children demonstrate intraclass correlation coefficients between 0.7 to 0.9 demonstrating excellent agreement [Urbina 2010]. We hypothesize that AIx, as measured by PWA, will be higher in individuals with higher triglyceride levels. AIx may also be an independent predictor of more rapid GFR decline.

6.4.2.2.2. Pulse wave velocity (PWV) measures the speed for the pressure wave generated by cardiac ejection to reach the periphery. PWV is a very reproducible measure, accepted as the most robust measure of arterial stiffness in pediatric studies [Urbina 2009]. PWV adds incremental information for risk stratification above and beyond measurement of traditional CV risk factors [Mitchell 2010, Cruickshank 2002]. It has been shown to be predictive of subsequent cardiovascular and cerebrovascular events in general population and in patients with CKD [Blacher 1999, Blacher 2003]. The SphygmoCor System (Atcor Medical, Sydney, Australia) measures pressure waves using a pencil-like probe placed on the neck, wrist, groin or foot pulse. The average of 3 sternal notch to distal artery of interest is entered. ECG R-wave gated arterial waveforms are recorded from the carotid then femoral artery. PWV is the difference in the carotid-to-femoral length divided by the difference in R-wave-to-waveform foot times. Higher PWV indicates stiffer conduit vessels. Reproducibility of PWV even in obese youth is < 7% [Urbina 2010]. We hypothesize that in cross-sectional analyses, children with CKD will have higher prevalence of increased PWV, signifying stiffer vessels. Additionally, PWV will be significantly correlated with higher LVM index, elevated BP, and lower GFR.

6.4.2.2.3 Heart rate variability (HRV) information will be collected with the SphygmoCor device using the same ECG electrodes previously applied for PWV. The subject will rest in the supine position for 10 minutes then have 10 minutes of resting ECG data collected for analyses. Heart rate variability (HRV) is a measure of variation in the beat-to-beat interval (RR intervals of electrocardiogram (ECG)). Analysis of HRV, as an index of autonomic regulation and clinical marker of evolving cardiac autonomic neuropathy is described in detail in a statement by the Task Force of the European Society of Cardiology [Task Force of the European Society of Cardiology 1996]. The SphygmoCor takes into account the normal heart beats, ignoring the ectopic beats, to derive the statistical parameters of the normal R-R intervals (NN intervals) of the ECG and estimates of several time and frequency domain HRV indices, the two most commonly used method for HRV analyses used to estimate sympathetic to parasympathetic nervous system balance. In one study of reproducibility in children, interobserver variability was 1% for all time domain measures and 4% for frequency domain measures [Batten 2000]. The gold standard measure for HRV is with 24-hour Holter monitors. In CKiD we have utilized ABPM to assess HRV, but this is limited as you can assess long term changes in HR but not short-term, minute-to-minute changes. The SphygmoCor device will give us minute to minute short term measures of HRV. We will examine the correlation between the ABPM and SphygmoCor assessment of HRV methods. We hypothesize that HRV will be lower in individuals with poor BP control.

6.4.2.3 Home Blood Pressure Monitoring

Pending funding, home blood pressure measurements will be collected using QardioArm, which is a wireless blood pressure device validated for measuring blood pressure and heart rate in participants with an arm circumference of 22-35 cm. At selected sites, a pilot study will be conducted in which home BP measurements will be collected to assess the feasibility of obtaining home BP measurements among CKiD participants who have not initiated RRT. Home BP monitoring will be performed beginning at visit 2 and then every year thereafter. Participants will be given the QardioArm device to take home to collect data over the course of 3 days.

6.4.2.4 Cardiac Magnetic Resonance Imaging (MRI)

To assess heart disease and conditions, cardiac MRIs will be performed on a sub-set of the cohort who are eight (8) years old or older at regular, irregular and post-RRT study visits. The cardiac MRI will be performed as long as the participant is able to tolerate the procedure without sedation. Deep sedation, general anesthesia or anxiolytics is not permitted. For participants who have not initiated RRT, it will be measured on children with a high probability of reaching ESRD. For these participants, the cardiac MRI will be performed at the next study visit after a participant reaches an estimated GFR less than or equal to 30 ml/min|1.73m^2, or at an irregular visit prior to the initiation of RRT, whichever occurs first. However, after the initiation of RRT, the cardiac MRI will be performed at post-RRT visits among participants who meet the age requirement regardless of their estimated GFR measurements. Refer to Section 5.4.4 for details regarding post-RRT (i.e., post-transplant and post-dialysis) visits.

6.4.3 Outcome Measures

An Outcomes Adjudication Committee will review potential cardiovascular hospitalizations using discharge summary and laboratory reports from these hospitalizations. If the clinical center determines that a cardiovascular event may have occurred during a hospitalization, a discharge summary will be obtained from that hospitalization and forwarded for distribution to the Outcome Adjudication Committee. The committee will then determine outcome status based on the discharge summaries. A cardiovascular outcome will include: sudden cardiac death OR hospitalizations for cardiomyopathy, congestive heart failure, and/or arrhythmias. Patient hospitalizations will also be reviewed for the occurrence of an increase in the dose of diuretics, ACE inhibitors or Angiotensin Receptor Blockers. Because children with CKD are unlikely to develop symptomatic cardiovascular disease, intermediate cardiovascular outcomes found during echocardiographic evaluation also will be evaluated. Specifically, new onset of LVH and LV dysfunction will be reported.

The primary outcomes will be the levels and within–individual changes of cardiovascular markers (e.g., Clinical BP, summary measures of echocardiography). Of particular interest will be the analysis of the association between decline in GFR and risk of progression of CVD as determined by changes in markers of CVD.

6.5 Growth Measures

CKD has a negative effect on linear growth, ultimately leading to decreased adult height in many patients. Along with affecting adult height, poor growth in children with CKD is associated with increased morbidity and mortality [Furth 2000, Furth 2002a, Furth 2002b, Wong 2000]. Finally, there is currently limited data on the influence of poor linear growth on neurocognitive and cardiovascular outcomes.

6.5.1 Core Tests

The core tests to measure growth are:

- Height/Length
- Body Mass Index
- Circumferences (Head, arm, waist and hip)
- Parathyroid Hormone (intact)
- High Sensitivity C-Reactive Protein
- Vitamin D
- Fibroblast Growth Factor 23 (FGF-23)
- Food Frequency Questionnaire
- Grip Strength

6.5.1.1 Height/Length and Body Mass Index (BMI)

Height/length and body mass index will be measured at every study visit for the entire cohort. Children will be measured in bare feet. Height will be measured using a stadiometer in all children > 2 years who can stand. Length will be measured in children less than age 2 or who are unable to stand by using a firm box in the supine position. If possible, parental height will also be measured at the first baseline visit (V1a).The techniques and equipment for measuring height/length will be reviewed with the principal investigator and study coordinator at each study site.

Height Standard Deviation Score (SDS) ([observed height – mean height for age]/height SDS for age) will be calculated based on chronologic age and gender using normative data for the US population. Linear growth will be evaluated as height SDS and change in height SDS over time. Change in height SDS will be expressed as annualized data. In addition, height velocity SDS will be calculated.

BMI will be calculated as weight (kg)/[height (m)]^2. Percentiles of BMI will be calculated using standard US charts.

6.5.1.2 Circumferences

Circumferences to be measured will include head and mid arm to the nearest 0.1 cm and, waist and hip circumference to the nearest 0.3 cm. At every visit, head circumference will be measured for children 3 years old and younger. Mid arm circumferences will be measured for the entire cohort. Waist and hip circumferences will also be measured for the entire cohort except for children 12 months old and/or younger who are unable to stand. The measure will use a tape with units of cm and not pinch or compress the tissue while taking measurements. More detailed descriptions of the procedures for circumference measurements and calculations will be included in the Manual of Procedures.

6.5.1.3 Intact Parathyroid Hormone (iPTH)

The ADVIA Centaur Intact PTH assay is a two-site sandwich immunoassay using direct chemiluminometric technology.

6.5.1.4 High Sensitivity C-Reactive Protein (hsCRP)

Given the increasing evidence for the importance of inflammation as a marker for mortality and declining albumin in patients with CKD [DeFilippi 2003, Eustace 2004, Kaysen 2004], inflammation may be an important variable affecting growth in children with CKD. High sensitivity CRP will be measured centrally at baseline and then every other year thereafter.

6.5.1.5 Vitamin D

Patients with CKD are at higher risk of vitamin D deficiency. They are also more likely to have lower levels of vitamin D in comparison to those with no kidney disease for a variety of reasons. We will explore the association between vitamin D deficiency and the risks associated with each of the scientific domains (CKD progression, growth, cardiovascular and neurocognitive and behavioral.) 25 Hydroxy Vitamin D will be measured centrally at baseline and then every other year thereafter.

6.5.1.6 Fibroblast Growth Factor 23 (FGF-23)

FGF-23 is a bone-derived circulating hormone and an important regulator of phosphate and vitamin D homeostasis. In adult CKD patients, increased FGF-23 concentration is a key factor associated with morbidity and mortality; however, the mechanism by which FGF-23 concentrations are increased in chronic kidney disease is unknown. We will explore the association between increased FGF-23 concentrations and growth retardation, CKD progression and risk factors for cardiovascular disease. FGF-23 will be measured centrally at baseline and then every other year thereafter.

6.5.1.7 Food Frequency Questionnaire (FFQ)

The Food Frequency Questionnaire was completed on a yearly basis beginning at the second baseline visit (V1b). During the study visit, the parents and/or child were instructed to complete the age appropriate FFQ and returned the completed form to the clinical site study coordinator. When the family returns the FFQ to the study coordinator, the study coordinator reviewed the forms for completeness. If there were missing information, the study coordinator clarified with the family and sent the completed FFQs to the Clinical Coordinating Center with the other study forms. As of the June 2014 amendment, the study discontinued collecting FFQ data.

6.5.1.8 6 Minute Walk Test (6MWT)

The 6 minute walk test was completed at visit 3 and then every year thereafter to measure functional capacity. The primary measurement of interest was the total distance walked. The study coordinators instructed the participant to walk as far as they can for six minutes. The 6MWT was done indoors in an appropriate corridor using cones to mark distance, or outdoors on a flat surface. The study coordinator recorded the distance walked, measured and recorded the participant's leg length and sent the data to the Clinical Coordinating Center. As of the June 2016 amendment, the study discontinued completing 6MWT.

6.5.1.9 Grip Strength Test

The grip strength test is used to measure maximal voluntary grip strength. For participants who are six (6) years old or older, a grip dynamometer will be used to measure grip strength at visit 3 and every other year thereafter.

6.5.2 Non-Core Tests

6.5.2.1 Physical Activity Monitoring

Pending funding, physical activity will be measured using an Actigraph Link device. The Actigraph Link device is an FDA-approved accelerometer frequently used for research purposes to assess physical activity. The device will be utilized to assess physical activity in a subset of participants at selected clinical sites. The device will collect 8 days of continuous wear data and monitoring will be performed at visit 1b and every year thereafter.

6.5.3 Outcome Measures

The core studies of this proposal will look at 2 principal questions. First, what variables affect growth? Second, does poor growth predict a poor outcome? The variables in the core study that may influence growth are listed in the following table:

Variables Affecting Growth

Variable	Method of Measurement
Pubertal status and BMI	Physical examination
Serum albumin (and urine protein), GFR	Laboratory measurement
Calcium, phosphorus, bicarbonate, CRP, PTH, vitamin D	Laboratory measurement
Gender and Race	History
Type and Length of kidney disease	History
Co-morbidities, surgeries, medications	History
Birth weight and height and gestational age	History
Parental heights	History and direct measurement
Grip Strength	Study form filled out by coordinator

Analysis will look at growth as the dependent variable using both current height SDS and growth velocity SDS.

The relationship between linear growth and the following outcomes will be analyzed: Neurocognitive Tests (Activity Level tests, Cognitive and Developmental Tests, Behavior Assessment Tests), Cardiovascular Outcomes (Hypertension, Left ventricular hypertrophy) and Morbidity and Mortality (Hospitalization Rate, Mortality). Analysis will focus on the relationship between current height (height SDS) and current growth velocity (height velocity SDS) and the various outcomes. In addition, the effect of covariates (e.g., inflammation, comorbidities) will be analyzed.

The data to be collected by CKiD will allow us to categorize the extent to which a decline in GFR is related to growth failure. The study has been designed to have the assessment of the changes in GFR precede the assessment of growth.

7. ANCILLARY STUDIES

To enhance the value of the CKiD study, the steering committee welcomes proposals from investigators to carry out ancillary studies. (See Section 3.8) Investigators are encouraged to submit proposals that deal with CKiD specific aims and associated hypothesis. Ancillary studies enable investigators to address questions of scientific relevance. Due to financial constraints, these studies were unable to be included as either core or non-core measures. CKiD has identified studies of interest that are related to the four specific aims and pending funding these proposed ancillary studies will be conducted.

7.1 Proposed Kidney Disease Progression Ancillary Studies

The followings areas are of high scientific importance to CKiD and will be given priority pending availability of funds: proteinuria, cytokines, genetics, renal reserve and renal fibrosis. In addition, participation of CKiD participants in studies such as the Pediatric Patient Report Outcomes in Chronic Disease (PEPR) Consortium, sponsored by the National Institute of AMS (NIAMS), will be optional. The purpose of PEPR, is to evaluate the validity of the Patient Reported Outcome Measurement Information System (PROMIS) by measuring patient experiences in clinical care and research in children with chronic diseases with a specific focus on chronic kidney disease, inflammatory bowel disease, and cancer.

7.1.1 Proteinuria: High Molecular Weight and Low Molecular Weight

Proteinuria is the consequence of two pathologic mechanisms, the abnormal transglomerular passage of proteins due to increased permeability of the glomerular capillary wall, and their subsequent impaired re-absorption by the epithelial cells of the proximal tubules. In glomerular diseases, the severity of the disruption of the structural integrity of the glomerular capillary wall correlates with the area of the glomerular barrier being permeated by the “larger” pores, permitting the passage into the tubular lumen of high-molecular-weight (HMW) proteins, to which the barrier is normally impermeable. The increased load of such proteins in the tubular lumen leads to the saturation of the re-absorptive mechanism by the tubular cells and to their toxic damage, which favors the increased urinary excretion of all proteins, including low-molecular-weight (LMW) proteins, which are completely reabsorbed under physiologic conditions.

Early studies have shown that in all glomerular diseases, the amount of total proteinuria and intermediate-molecular-weight (IMW) proteinuria such as albuminuria is a powerful predictor of the progression to end-stage renal disease (ESRD). In more recent studies, the urinary excretion of HMW, and LMW proteins correlates with the severity of the histologic lesions and may predict, better than total or IMW proteinuria, the natural course, the outcome and the response to treatment. Specifically, HMW proteinuria is associated with segmental sclerosis and LMW proteinuria is associated with tubulo-interstitial damage on renal biopsies from patients with primary glomerulonephritis [D'Amico 2003].

Some potential ancillary studies on proteinuria include:

1. To determine if HMW proteinuria (IgG) and LMW proteinuria (1-microglobulin) predict, better than total proteinuria and IMW proteinuria(albuminuria), the deterioration of GFR in children with CKD.
2. To determine if novel urinary biomarkers by urine proteomics studies predict the deterioration in GFR in children with CKD.

7.1.2 Cytokines

Minimal attention has been focused on the presence of inflammation and oxidation as risk factors for the accelerated progression of CKD and the early development of atherosclerosis in children. Recent work regarding inflammatory responses in children with CKD has demonstrated vascular cell adhesion (sVCAM-1) and soluble intercellular adhesion molecules (sICAM-1) are high in children with CKD (stages I-III) versus healthy controls [Musial 2002]. Atherosclerotic-related morbidity and mortality is also strongly predicted by both IL-6 and C-reactive protein (CRP) [Harris 1999,Pecoits-Filho 2002,Ridker 2000,Ridker 1998]. Specifically, inflammation increases as CKD progresses, such that IL-6 and CRP levels have been inversely associated with declining renal function, with CRP highest when GFR<20 mL/min [Panichi 2001]. Furthermore, quantification of oxidative stress, standard lipid panels, and inflammatory markers [Besbas 1998, Bolton 2001, Stenvinkel 2000] will provide important data from which to elucidate the enhanced atherogenic milieu that children with CKD may chronically demonstrate as their kidney disease remains stable or progresses. Therefore, pending ancillary funding, inflammatory and markers of oxidative stress will be addressed.

7.1.3 Genetics

Differing incidence rates of CKD in racial and ethnic populations, and familial aggregation studies have consistently pointed to a genetic susceptibility to the risk of progressive CKD [Bowden 2003]. A number of candidate genes have been tested and have been shown to be associated with kidney disease progression, particularly genes which code for cytokines, growth factors, and nitric oxide syntheses. These types of candidate gene studies are now being complemented by genome scans that give a comprehensive evaluation of inheritance in kidney disease families, and Transmission/Disequilibrium Tests (TDT) that test for linkage between a complex disease and a genetic marker, using nuclear family data [Bowden 2003]. Genetic predisposition will be measured in future ancillary studies using banked DNA. The steering committee will need to consider the utility of obtaining DNA from parents at the same time that blood is obtained from enrollees, for future studies of genetic susceptibility to progression.

7.1.4 Renal Reserve

Future ancillary studies may use the iohexol plasma disappearance procedure to measure short-term increments in GFR [Nilsson-Ehle 1994]. Since the infusion of 10 ml iohexol can be detected for at least 12 hours after infusion into normal subjects [Nilsson-Ehle 1994], the protein loading studies can be performed after the same infusion of iohexol. In this case, after the two-sample determination of GFR (3-5 hours)

a protein meal corresponding to 2 g/kg of cooked meat or 1 gm protein/kg of Nepro (70 g protein/L or 14.3 ml/kg body weight) is administered over 20-30 min [De Santo 1997, Englund 2000]. Provider should use acceptable vascular access. Blood sampling can be performed after inserting a second polyethylene catheter. A second set of blood samples for iohexol would then collected at 2 and 4 hours after the protein load.

7.1.5 Renal Fibrosis

Most experimental and human renal diseases progress to ESRD often independently of the events responsible for the initial lesion. Histologically, progression of renal disease is characterized by both glomerulosclerosis and tubulo-interstitial fibrosis. Pending future funding studies to assess renal fibrosis will be conducted.

7.1.6 Novel Biomarkers for Pediatric CKD Progression

Recent advances in laboratory techniques available to study the nature and variety of plasma metabolites and proteins (metabolomics and proteomics) hold great promise for the discovery of highly discriminant biomarkers of and new potential therapeutic targets for varied diseases. However, these techniques have not been applied in children with chronic kidney disease. Congruent with the overarching specific aim of the CKiD study to identify novel risk factors for the progression of CKD in children, the Chronic Kidney Disease Biomarkers Consortium (CKD BioCon), will utilize existing samples from the NIDDK repository to perform state of the art metabolomic and proteomic profiling for the discovery and validation of novel biomarkers of CKD progression in children.

Participants with samples in the NIDDK Repository have already consented for these samples to be used for future research of CKD. The samples in the Repository are coded and do not have any personal identifiers i.e. name, social security number, medical record number or date of birth.

7.2 Proposed Neurocognitive Ancillary Studies

Pending future funding CKiD will conduct the following tests:

- Diagnostic Interview Schedule for Children (DISC)
- EEG
- Brainstem Auditory Evoked Response

7.2.1 Diagnostic Interview Schedule for Children (DISC)

The Diagnostic Interview Schedule for Children (DISC) is a highly structured psychiatric diagnostic interview which yields DSM-IV diagnoses with extensive reliability in epidemiological and clinical populations. The DISC is available in both Parent and Youth versions. The Parent version is available for ages 6-17, and the Youth self-report version is available for ages 9-17. The test is computer assisted, and can be administered by non-medical personnel after training. Both the parent and youth versions take 90 minutes to complete. Given the extensive amount of time that each of these structured interview procedures requires, we will employ a “trigger” mechanism to indicate when these structured interviews should be conducted. This trigger mechanism will involve the summary scores on either the BASC. Pending funding DISC will be administered.

7.2.2 EEG

Cerebral cortical function may be assessed electrophysiologically using the EEG or by recording cognitive evoked potentials such as the P300 and the mismatch negativity. The EEG can be assessed by visual inspection by an experienced electroencephalographer or by using quantitative EEG analysis techniques. In the latter, the Fourier transform is used to covert the voltage-versus-time EEG waveform into an amplitude- or power-versus-frequency waveform. The frequency range is typically divided up into bands, and the EEG power over a band is integrated to give a single total power value for that band, e.g. alpha power or delta power. Ratios, such the alpha/delta power ratio, are also useful in assessing for cerebral dysfunction.

EEG changes in patients with renal failure typically show background slowing, including slowing of the dominant background rhythms (such as the alpha rhythm) and the presence of superimposed slow waves that are even lower in frequency. The degree of EEG slowing correlates with biochemical measures of the severity of uremia [Bourne 1975]. Among those with severe uremia, the EEG may also show intermittent or transient EEG findings such as frontal intermittent rhythmic delta activity (FIRDA), spike-and-wave discharges, or triphasic waves. In patients undergoing dialysis, the most important predictors of dialysis encephalopathy are FIRDA and spike-and-wave discharges background [Chokroverty 1982].

Ancillary studies of EEG will be recorded with the subjects awake and relaxed with their eyes closed, in order to assess the alpha rhythm. The EEG recordings will be reviewed by experienced electroencephalographers to identify background or intermittent abnormalities. Spectral analysis will also be performed on the EEG data. For this reason, all EEG data must be acquired using digital EEG machines.

7.2.3 Brainstem Auditory Evoked Responses (BAER)

Function of central white matter tracts is evaluated by recording sensory evoked potentials. Visual, auditory, and somatosensory evoked potentials have all been studied in patients with ESRD. Brainstem auditory evoked potentials (BAEPs) are typically elicited by presenting brief acoustic stimuli, such as clicks, through headphones and recording the responses with latencies less than 10-15 msec. A series of peaks is obtained (waves I, III, and V are the most consistent peaks) which reflects neural activity in the distal eighth nerve and at various points along the brainstem auditory pathways. The interpeak intervals therefore provide a measurement of conduction through central white matter pathways (the auditory nerve is included, but along most of its length the axons within the auditory nerve are ensheathed by central nervous system-type myelin, produced by oligodendrogliocytes. Prolonged I-III interpeak intervals, which reflect delayed neural conductions between the distal eighth nerve and the lower pons, were commonly found in patients with ESRD, including those on hemodialysis, in most published studies [Gafter 1989, Pratt 1986], but not in all of them [Hurkx 1995]. The I-III interpeak intervals may change acutely after dialysis, possibly due to changes in the patient's calcium level [Pratt 1986]. Prolonged III-V interpeak intervals, reflecting delayed neural conductions between the lower pons and the mesencephalon, are also seen in patients with ESRD; these do not change acutely after

dialysis [Komsuoglu 1985]. BAEP abnormalities in patients with ESRD are not corrected by successful treatment of anemia with erythropoietin [Suppiej 1992].

All three evoked potential modalities may be used to test for central white matter conduction abnormalities in ESRD. However of the three (Flash VEPs, SEPs and BAEPs), BAEPs are easy to perform and painless, and they require no subject cooperation except for relaxation. Therefore BAEPs will be the modality used in ancillary studies.

7.2.4 P300 Cognitive Event-Related Potential

Cognitive event-related potentials differ from the aforementioned sensory evoked potentials in that they are produced when the subject performs a sensory discrimination task. A series of stimuli that differ in some attribute (such as a series of tone pips of various frequencies) are delivered, and the subject is asked to identify a particular stimulus when it occurs. Identification of the target stimulus is typically accompanied by a scalp positivity at a latency of about 300 msec, labeled the P300. P300 component latencies are commonly prolonged in patients with renal failure [Cohen 1983,Kramer 1996,Sagales 1993], including in patients who are neurologically asymptomatic [Evers 1998]. The amplitude of the P300 component typically increases, and its latency typically decreases, following hemodialysis [Evers 1998, Gallai 1994, Tennyson 1985]. Following transplantation, the latency and amplitude of the P300 typically improve to the normal range [Kramer 1996].

Recording of the P300 requires subject cooperation with the sensory discrimination task. In the auditory modality, infrequent "oddball" stimuli that are presented following several repetitions of a standard stimulus may elicit a cerebrally-generated component labeled the "mismatch negativity", even if the subject is not performing a sensory discrimination task. This may assess similar cortical mechanisms to the P300, involving short-term memory and comparison of different stimuli. However, the mismatch negativity is smaller and more difficult to record than the P300. Pending additional funding P300 will be performed in future ancillary studies.

7.3 Proposed Cardiovascular Ancillary Studies

There are several measurements of known or suspected significance in CVD that must be deferred for stored sample analysis and will require additional resources not currently available. Stored serum, plasma and genetic materials will be used for proposed future ancillary studies of:

1) Apolipoprotein Analysis- The major apo’s include Apo B, Apo A-I, Apo A-II, Apo C-II, Apo C-III, Apo E, as well as Lipoprotein(a) (Lp(a)), and associated proteins such as cholesterol ester transfer protein (CETP), and the enzymes lecithin-cholesterol acyltransferase (LCAT), lipoprotein lipase (LPL), and hepatic lipase (HL).
2) Lipoprotein particle number and size distribution as assessed by NMR analysis.
3) Homocysteine and metabolically related products
4) Metabolic Syndrome of Insulin Resistance – Abnormalities encountered in CKD overlap substantially with the so-called “metabolic syndrome,” which is singled out as a major risk factor for CVD [Adult Treatment Panel III 2001]. The central feature of the metabolic syndrome is insulin resistance (hyperinsulinemia), which is also a

well-described, highly prevalent feature of CKD Other associated abnormalities of the metabolic syndrome include obesity, dyslipidemia, hypertension, and hypercoaguability [Ginsberg 2003]. Given the array of known biochemical similarities shared with CKD, it is highly suspected that measurements of markers of the metabolic syndrome are associated with CVD or CKD progression. Potential markers for ancillary studies will be measurement of insulin and (preserved) glucose levels.

7.4 Proposed Growth Ancillary Studies

A variety of additional tests related to growth, nutritional status, and renal osteodystrophy in children with CKD will be the subjects of ancillary studies pending additional funding.

7.4.1 Inflammation

Markers of inflammation have been shown to correlate with declining nutritional status, morbidity and mortality in adult patients with CKD. CRP will be a core test, but a variety of other inflammatory markers may ultimately prove to be more informative. Inflammatory markers will be studied for their relationship to indices of nutrition (e.g., albumin, BMI), linear growth and renal osteodystrophy. Examples of potential inflammatory markers that could be examined in ancillary studies include IL6, TNF, CRP, IL1, RANK-L and OPG.

7.4.2 GH/IGF-1 Axis

The GH/IGF-1 axis is dysfunctional in CKD, but there is currently no understanding of the relevance of serum markers of this system to the management of children with CKD, especially related to the need to initiate rhGH therapy. Moreover, we have inadequate understanding of the mechanisms whereby perturbations in this system cause growth retardation in CKD. Ancillary studies may examine the various components of the GH/IGF-1 axis (GH, IGF-1, free IGF-1, IGFBP3 fragments & protease activity, IGF-1 binding proteins 1-6, ALS) and relate them to linear growth, response to rhGH therapy and other markers (such as PTH or inflammatory markers).

7.4.3 Hormones

A variety of other hormonal systems influence growth and nutrition, and may be the subjects of ancillary studies. These include thyroid hormone, alpha-melanocyte-stimulating peptide, ghrelin and leptin, which are all known to be abnormal in CKD. Additional studies may examine sex hormones, such as testosterone and estrogen.

7.4.4 Nutrition

The core measures of nutrition include albumin, BMI and cholesterol. Ancillary studies may analyze additional nutritional measures (e.g., pre-albumin, insulin, serum branch-chained amino acids, transferrin). Such markers may be more predictive of outcomes such as declining growth, poor response to rhGH or decreasing BMI. In addition, an ancillary study may use DEXA to determine lean body mass and total body fat in a cohort of patients.

7.4.5 Bone

Both for the full cohort and especially for children in which bone biopsy data has been obtained, additional measures of bone, calcium, and phosphate metabolism may provide data that will be useful in understanding the mechanisms of disordered mineral metabolism and renal osteodystrophy in children with CKD. Serum measurements may include ionized calcium, alkaline phosphatase, 25-vitamin D, 1,25-vitamin D, osteocalcin, second generation immunometric PTH assay [recognizes only PTH (1-84) and possibly PTH fragments that are truncated at the carboxyl-terminus, but not PTH (7-84)], and FGF-23. Urine testing may include type I collagen N-telopeptide, phosphorus and creatinine. In addition, bone density by QCT will hopefully be obtained in the bone biopsy cohort.

8. ANALYSIS, INTERPRETATION, AND PRESENTATION OF DATA

8.1 Data Analysis Plan

To answer the scientific research questions, we will employ a combination of classic and modern data analytic approaches as outlined in the 1998 issue of *Epidemiologic Reviews* dedicated to cohort studies and co-edited by A. Muñoz. We will use state-of-the art data visualization tools and statistical graphics to conduct exploratory analyses and enhance presentations of data and analytical results. Because of its prospective nature, this cohort study will necessitate the development and use of analytical methods in the areas of longitudinal and survival data analysis [Muñoz 1998].

Principal outcomes to measure the progression of kidney disease in children are two-fold. The first principal outcome is the rate of decline of the biomarker GFR, which is measured repeatedly over time in cohort participants. The second principal outcome is the time-to-ESRD, defined by transplantation, dialysis, or when GFR reaches a pre-specified threshold level (GFR <15 ml/min|1.73m^2). The analysis of rate of decline as the outcome of interest requires the use of methods for longitudinal data; the analysis of time-to-ESRD requires the use of methods for survival analysis. The two approaches are closely related, in part because rapid progressors are characterized by a high rate of decline and short times-to-ESRD, while slow progressors are those with lessened decline and relatively long times-to-ESRD.

The outcomes to measure the effects of CKD on neurocognitive function, profile of risk factors for cardiovascular disease and growth will also be changes in biomarkers over time. For neurocognitive function we will use changes in the constellation of tests that will be used to measure cognitive function and behavior. In addition to the standard challenges of analyzing longitudinal data, the neurocognitive data will be multivariate in nature and different tests will be used in different ages. In order to identify domains and canonical dimensions, we will use multivariate methods to appropriately combine the information provided by the constellation of tests. By design, we have selected the tests that at different ages are designed to measure common features. Features of specific ages will be analyzed as levels, not as longitudinal changes, using standard regression methods.

Changes in blood pressure (obtained by either ambulatory blood pressure procedures or in the clinical setting) over time will be used to determine the effects of CKD on cardiovascular outcomes. Similarly, changes in height and iPTH are examples of outcomes to characterize the effect of CKD on growth.

We anticipate that there will be issues posed by the data for which available analytical methods will not be appropriate. A major effort by the investigators of the proposed KIDMAC will be to extend and develop novel analytical methods. It is expected that the study will be conducive to making contributions to the methodological literature.

8.1.1 Longitudinal Data Analysis of Biomarkers

The longitudinal data analysis methods described in this section apply with equal force to the analysis of the rate of decline in kidney function as measured by GFR, as well as to the level and rate of changes in standardized (i.e., z-score transformed) neurocognitive function, to the level and rates of change of blood pressure and fasting lipids, and to the level and rates of growth as measured by changes in height and weight. In addition, the methods of this section apply to the analysis of the rate of change in standardized neurocognitive function, the rate of change in markers of risk factors for cardiovascular disease and the rate of growth as predicted by preceding changes in GFR and other co-variables.

The description of trajectories of markers for kidney disease progression is the primary aim of specific aim 1. The first step for the analysis of longitudinal data is to determine the nature of the outcome (e.g., continuous, binary, count), and to choose the scale by which change is to be measured (i.e., original or transformed [e.g., log] scale). The use of the logarithmic transformation not only achieves normality of skewed distributions but also allows the use of percent change as the primary measure of decline, which is a particularly intuitive clinical measure.

Gaussian theory likelihood-based approaches are often appropriate for continuous responses; they are not directly applicable to responses that are binary or categorical (ordinal or nominal). We have experience with the application of several models for categorical data that include parameters to incorporate the within-individual correlation structure. These include the use of the beta-binomial model and its extension to general categorical responses, the Dirichlet-multinomial model [Gange 1996]. Alternate methods have also been proposed [Breslow 1993, Hedeker 1994], and we have access to software for implementing these methods.

An important issue of longitudinal data is the intrinsic dependence of the observations measured over time within individuals. Analyses can deal with this dependence in different ways [Diggle 1994, Pendergast 1996, Ware 1988]. When scientific questions are focused only on modeling the mean structure, an appealing approach is to treat the dependence as a nuisance parameter. This is the approach taken by generalized estimating equation (GEE) methods [Liang 1986], which are applicable to a wide array of problems. KIDMAC investigators have extensive experience with and ready access to software for these methods for continuous, count, and binary outcome variables, as well as for ordered categorical data [Gange 1995].

Modeling the dependence structure in longitudinal data may yield clinical insight. These models, called mixed models or random coefficient models, allow intercepts and slopes for given individuals to deviate from the group averages according to variance components (i.e., within- and between-individual variances); thus, the model takes into account the correlation of the repeated observations obtained over time for each individual. These methods also allow for inclusion of individuals with varying numbers of data points. For continuous linear outcomes, we have extensive experience using the MIXED procedure in SAS [Littell 1996], which provides a number of methods for specifying a particular correlation structure. KIDMAC investigators [Muñoz 1992]

developed a general regression model that incorporates a flexible correlation structure over time, where the autoregressive (AR1) and compound symmetry (CS) models are special cases. This strategy provides parameters that parsimoniously describe the correlation structure, and it allows formal testing, using likelihood ratio statistics, of whether a simpler AR1 or CS structure is appropriate for the data. Studies have demonstrated that several biomarkers of disease progression (e.g. blood pressure, CD4 cell count, FEV1) are best modeled with a structure intermediate between an AR1 and CS structure [Beckett 1992, D'Agostino, Jr. 1995, Galai 1993]. For nonlinear outcomes, we have experience using the NLMIXED procedure in SAS, which provides a general maximization procedure. A key feature of methods for longitudinal data is the ability to incorporate incomplete and unbalanced data [Schluchter 1988].

Informative censoring may bias naïve analyses. A joint model is a model for two or more different outcomes. The goal of such modeling is the study of relationships between exposures and distinct but related outcome processes. For longitudinal data, a joint model must take account not only of the dependence resulting from repeated measurement of the same outcome, but also of the association between the different outcomes, all measured on the same individual. An example is a joint model for longitudinal and survival data, although the family is much broader than this.

We denote the two outcome vectors simply by Y_1 and Y_2. A desired approach is to directly model the joint distribution, $f(y_1, y_2)$. This would at first seem difficult, since the required dependence structure would appear to be quite complex. A solution to this problem has been provided by the development of shared-parameter models, in which the necessary dependence structure is provided by a vector of shared random effects, b, which links all the measurements on the same individual. Typically the two outcomes are assumed to be independent given the random effects, which results in a relatively simple factorization of the joint likelihood, $f(y_1, y_2, b) = f(y_1 \mid b)\, f(y_2 \mid b)\, f(b)$. Parametric models for the marginal distributions of each outcome, as well as the standard assumption of a multivariate normal distribution for the random effects, provide a complete description of the joint likelihood. These models have the non-missing at random property [Albert 2009]. Statistical software to fit these models is now available in standard statistical software packages such as SAS and Stata. The marginal likelihood of the observed data is obtained by computing the marginal distribution, $f(y_1, y_2) = \int f(y_1, y_2 \mid b)\, f(b)\, db$. The identical random effects are not required to appear in each of the marginal models. It is sufficient if these effects are distinct but correlated through their joint distribution. This possibility provides considerable additional flexibility for shared-parameter models.

As an example, we consider the important special case of informative dropout, when subjects leave the study for reasons related to the effects of exposures and/or the progression of disease. This example is especially important for the CKiD study, since a number of dropouts have already occurred when participants require dialysis or kidney transplant, presumably due to the progression of their disease. In this case the vector Y_1

consists of longitudinal data on the continuous outcome GFR, while $Y_2 = T$ is the time to dropout. Under the additional assumption that the components of Y_1 are independent given the random effects, the density of the longitudinal data can be factored as the product of the densities of the observed and unobserved data, $f\left(y_1 \mid b\right) = f\left(y_1^o \mid b\right) f\left(y_1^m \mid b\right)$. The missing data y_1^m can then be integrated out of the joint likelihood, and the marginal distribution of the observed data, $f\left(y_1^o, t\right)$, can be written as a joint model $f\left(y_1^o \mid b\right) f\left(t \mid b\right) f(b)$ marginalized with respect to the random effects.

Shared-parameter models clearly offer a useful approach to the problem of informative missingness, and it is anticipated that they will play a significant role in future analyses of longitudinal data from the CKiD study

Modelling GFR trajectories as nonlinear may provide additional insight. GFR decline has been approximated as log-linear in most analyses of progression, an assumption that has been consistent with available data [Mitch 1976; Hunsicker 1997]. However, many studies rely on relatively short follow-up and few repeated measures. Given the convenience of assuming a linear GFR trajectory resulting from the ease of modeling and interpreting linear slopes, few studies have sought to validate the linearity assumption and explore the possibility of nonlinear GFR decline. However, heterogeneity in GFR trajectories and the implications on the risk for adverse outcomes is of great interest [Levin 2012]. Clinical strategies and even patient response to care could potentially benefit from new insights into the variable paths of progression of CKD [O'Hare 2012; Schell 2012]. The challenge is in describing nonlinear pathways and heterogeneous progression in a way that provides scientific rigor [Levin 2008] but also lends itself to clinical utility.

One study by Li and collaborators [Li 2012] that examined GFR trajectories used Bayesian smoothing splines to capture nonlinearity. These methods will be explored as our data on GFR trajectories matures through the next funding cycle to elucidate patterns in individual pathways of progression that are clinically informative and could lead to improved treatment, slowing of prevention, or improved outcomes. However, using the data collected by CKiD up to July 2012, we can test whether modeled trajectories are different from an expected trajectory given no proximate renal replacement event using a case-control design whereby each case (i.e. a child observed to go to RRT) is matched individually to a single control (i.e. a child not *yet* observed by the time of the case to go to RRT) on the basis of GFR at CKiD study entry, diagnosis and time under observation. Using mixed models with spline terms we can explore deviations from linearity in the case group prior to RRT. The model would take the form:

$$y_{ijk} = \left(\beta_0 + a_i + d_j\right) + \left(\beta_1 + b_i\right) t_{ik} + \left(\beta_2 + c_i\right)\left(t_{ik} - m\right)_- + \beta_3 case_j + \beta_4 t_{ik} case_j + \beta_5 \left(t_{ik} - m\right)_- case_j + \varepsilon_{ijk}$$

with a_i, b_i, c_i representing the individual deviations of the intercept, slope and spline; d_j the clustering of case-control pairs; *m* the spline knot ; and ε_{ik} the random error.

Causal modelling strategies can provide better comparisons for evaluating treatment effectiveness. Randomized clinical trials are typically considered a standard study design for inference of the causal effect of an exposure on an outcome. However, when the exposure is predicted to be detrimental to health (e.g., abnormal birth history), an observational study design is a suitable choice to investigate the effect of the exposure on an outcome. Established methods are available to attempt to mimic randomized experiments for the purpose of estimating causal effects in observational studies. These approaches include propensity score matching methods [Stuart 2010], inverse probability weights based on propensity scores [Robins 2000] and marginal structural models [Hernan 2001]. The guiding principle of these approaches is to construct a sample in which two or more groups (e.g., exposed/unexposed) have identical (or balanced) distributions of confounders [Stuart 2010; Cole 2003]. Many CKiD scientific initiatives have presented research questions involving strong confounders for which these approaches may be appropriate. Propensity score matching methods are one strategy for investigating the putative effect of an exposure on an outcome. The analysis comprises two phases: the first phase generates propensity scores (i.e., each subject's probability of being exposed) for the purpose of constructing a weighted unexposed sample with similar confounder distributions as the exposed group; the second phase uses the weights to assess the causal impact of exposure on the outcome.

A second strategy is the use of Inverse probability weights. There is growing interest in determining the effectiveness of the many therapies that children with CKD receive, but there is strong confounding by indication as therapies tend to be given to individuals who fulfill guidelines for who and when to treat. Standard regression adjustments to compare outcomes of treated to those untreated seldom achieve control for the indication for receiving treatment. Alternative approaches include the use of inverse probability weights (IPW) based on probability of receiving treatment. IPW estimators provide an excellent means for estimating the causal effects of treatment among individuals with different covariate values at study baseline [Robins 2000]. However, covariates are often dynamic and changing values may alter the impact of therapy on the outcome. IPW methods offer powerful tools to deal with complex patterns of confounding, particularly in longitudinal data, where outcomes at one time point may influence both subsequent treatments and outcomes. In particular, marginal structural models have been proposed to deal with patterns involving feedback such as this. The weights in these models are updated longitudinally using the complete past history and are stabilized to improve performance. Marginal structural models and their variants such as G-computation have become staples for dealing with problems involving time-varying confounding. These methods will be explored for the analysis of longitudinal data from CKiD.

However, marginal structural models can be limited in their flexibility, becoming unstable if certain covariate values yield very large or very small probabilities of treatment. Structural nested mean models [Robins 1994] provide a mechanism for estimating the direct effect of treatment on an outcome, taking into consideration the entire covariate and treatment history. These models are complex but can be implemented with standard software (e.g. SAS PROC NLP, SAS Institute). A more user friendly alternative

is the recently proposed history adjusted marginal structural model [Petersen 2007], which assumes a standard marginal structural model at each time point of the study. These models are best used with moving windows of data such that a fixed time interval is established between the assessment of covariates for the inverse probability estimator and the outcome [Robins 2007].

8.1.2 Analysis of Time-to-Event Data

In the proposed cohort study, several time-to-event outcomes of potential interest are (1) ESRD, (2) transplantation, (3) the initiation of dialysis, (4) GFR falling below 15 ml/min|1.73m^2, and (5) a pre-specified reduction (say 50%) in GFR. The survival analysis methods described in this section apply with equal force to each of these endpoints of interest and represent an important component of the armamentarium to address the study aims.

The use of time-to-event methods in cohort studies requires considerable attention to the underlying assumptions and censoring mechanisms. One particular issue concerns the incompleteness of outcome data. Careful consideration should be given to the censoring strategy, since censoring at the last time individuals were seen could lead to biased estimates if cases are actively sought and collected up to the date of the analysis [Muñoz 1997]. For instance, were event ascertainment complete, it would be more appropriate to censor follow-up time at the date of analysis [Hoover 1993], rather than at the date last seen. For most studies, an appropriate censoring strategy will be somewhere between these two extremes (i.e., the last contact and the date of analysis). The optimal approach will depend on the study design developed by clinical investigators in concert with KIDMAC investigators. For the analysis of time-to-ESRD, the trajectories of censored observations can be used to estimate when an individual will reach the threshold that defines an event. In doing so, we will circumvent informative censoring since we will use internal data to complete the missing information of when an individual reaches the threshold that defines an event. The complementary use of methods for longitudinal data and survival analysis will be a subject of methodological research by KIDMAC investigators.

Analytical Methods using Time since CKD Diagnosis as the Time Scale. The most common time scale for the analysis of data from cohort studies is the time since entry into the study, with analysis typically carried out in strata determined by biomarkers of disease progression (e.g., GFR). However, this may not be the most appropriate timeline for analysis. A more natural approach is to consider the time axis as the duration of disease, incorporating the time from CKD onset until the date of the baseline visit as late entries to avoid survivorship bias. Under a Generalized Gamma (GG) distribution [Cox 2007], the likelihood function can easily accommodate the data incompleteness embodied in late entries and censored times. Due to the relatively long times since CKD diagnosis at study entry for many of the participants, we can restrict the analysis to the occurrence of RRT after 2 years from the CKD diagnosis. It will be important to continue to recruit children with glomerular disease, who are more likely to enter the study shortly after their diagnosis, and very young children with non-glomerular disease, who are most frequently diagnosed at birth in order to inform the early portion of the survival curve proximate to CKD diagnosis. The data to be collected

by CKiD during the funding cycle of this renewal application will be conducive to obtaining a more complete picture of CKD progression, especially in the time interval immediately subsequent to CKD diagnosis.

Parametric survival methods may provide clinical insight about the underlying disease process. Semi-parametric methods are of limited use for the estimation of the rate of disease itself and for quantifying the effect of an exposure in terms of the contraction (or expansion) of the disease-free time that an exposure induces. To estimate such measures, we propose to use a variety of parametric approaches, such as modeling times using lognormal, Weibull, or Gamma distributions [Muñoz 1996b, Piantadosi 1995]. Parameters defining the shape of these distributions can be modeled as a function of covariates, and standard likelihood inferences and goodness-of-fit tests can be made. KIDMAC investigators have successfully applied parametric survival methods for the analysis of HIV/AIDS data and bronchial responsiveness [Muñoz 1996a, Muñoz 1996b]. Methodologically, the analysis of bronchial responsiveness has commonalities with the analysis of chronic kidney disease. Namely, the outcome of interest is the time a marker takes to reach a threshold. As discussed by [Muñoz 1996a], when the event is the crossing of a threshold by a marker, the degree by which the threshold is surpassed contains information for when in between two discrete visit dates the threshold would have been achieved had intermediate visits occurred. Such information is of use to calculate the actual but unobserved event time.

Treating competing risks appropriately may increase clinical understanding. Competing risks methods have been utilized in CKiD to investigate differences in progression to dialysis and transplant. Two major approaches to competing risks are the cause-specific hazards method, which partitions the total hazard as the sum of mutually exclusive cause-specific hazards [Putter 2007], and the sub-hazards method, which partitions the total cumulative incidence as the sum of mutually exclusive cause-specific cumulative incidences, each with its own underlying sub-hazard [Fine 1999]. A typical application of these methods involves a single binary covariate, such as baseline urine protein:creatinine ratio above or below 2, which divides the cohort into two groups and leads to the estimation of relative hazards. Often, regardless of the approach chosen, an assumption of proportionality of hazards is made to simplify the analysis. However, this assumption may lead to erroneous conclusions if violated. Specifically, if the sub-hazards for both events are assumed to be proportional, the two relative sub-hazards must lie on opposite sides of 1; but independent estimation methods do not account for this, and results may not adhere to this requirement.

The relative cause-specific hazards and relative sub-hazards are inextricably linked to the cause-specific cumulative incidences, and are therefore tethered. In particular, proportionality cannot simultaneously hold for all hazard types [Beyersmann 2012]. The simplest way to avoid incongruent results is to eschew the proportionality assumption and include time dependency in the model. This adjustment is easily implementable in software with competing risks packages such as STATA and R. Models free from the assumption of proportionality are more appropriate for the complexities of the associations between exposures and outcomes, and often provide a clearer depiction of

the time-dependent effects of exposures on the competing endpoints than simply estimating a time-averaged effect.

8.1.3 Analytic Method of Nested Studies

It is expected that numerous hypotheses about pathogenesis of kidney disease will be investigated within the study. Many of these hypotheses will involve highly technical, and, in some cases, expensive and time-consuming laboratory assays. For this reason, and because the study populations will often be very specific, it will not be possible to investigate these scientific questions in the full cohort. To make efficient and scientifically meaningful comparisons in such situations, it will often be necessary to either: 1) identify cases and match them to controls based upon specific characteristics to perform nested case-control analysis, or 2) select a sub-cohort in which to perform a case-cohort analysis.

KIDMAC will provide essential design and analytic support to these projects to ensure that the scientific questions can be addressed and that appropriate inferences are drawn from the data. These activities require not only epidemiological and statistical expertise, but rely upon the proposed leadership of KIDMAC in the area of study coordination as it relates to the efficient tracking and accessing of samples from the national repository. In nested case-control studies, we will make extensive use of conditional logistic regression for determining factors associated with case status in the study pathogenesis studies. We will ensure that matching is done according to appropriate epidemiologic principles such that potential controls for each case have been followed for at least as long as the case, to ensure that they had equal opportunity to develop the outcome that determines case status. In case cohort analyses, we will use a weighted estimating equations approach [Barlow 1999].

8.2 Examples of Aim-Specific Analyses

Below, we describe specific analyses for examining the associations of decline in kidney function on the levels of and changes in biomarkers for specific aims related to neurocognitive development, cardiovascular disease, and growth.

8.2.1 Intelligence Quotient

The intelligence quotient (IQ) is a general and stable indicator of general cognitive functioning that will be validly and reliably measured on children 30 months and older in CKiD. Let Y_{ij} be the IQ as derived from the WPPSI-III for children aged 30 months to 5 years, or the WASI for children aged 6 to 18 years for child i at visit j, where visit j is taken at time t.

A regression of the form $Y_{ij} = b_0 + b_1t_{ij} + b_2G_{ij} + b_3G_{ij}t_{ij}$, where the variable G_{ij} is the decline of GFR in the preceding year scaled to a 5-unit difference (= $(GFR_{ij-1} – GFR_{ij})/5$), will describe the trajectory of cognitive functioning as a line with intercepts b_0 for those with no GFR decline and $b_0 + b_2$ for those with a 5 ml/min|1.73m^2 decline in GFR, and slopes b_1 for individuals who have no GFR decline and $b_1 + b_3$ for those with a 5 ml/min|1.73m^2 decline in GFR. Here, the intercepts describe the initial difference in IQ due to decline in GFR, and the slopes describe the linear rate of change in IQ due to decline in GFR. Since this study is planning to measure GFR every two years, we will

either annualize the change in GFR over the preceding two years for which the observed data will be available or we will estimate the GFR not measured directly in a given year using the serum creatinine which will be available every year. Specifications other than the annual difference in GFR will be explored. Also, we will be able to investigate nonlinear changes in IQ over time by a polynomial expansion of t_{ij} into say the cubic function $t_{ij} + t^2_{ij} + t^3_{ij}$. The intrinsic statistical dependence of repeated IQ measurements taken on individuals will either be included as additional parameters using mixed effects models or will be treated as a nuisance using generalized estimating equations.

The above regression will be extended to control for possible confounding by age since diagnosis and socioeconomic status by the addition of b_4A_{ij} and b_5SES_{ij}, where A_{ij} is the percent of a child's age that the child has lived with CKD centered about 50% (= [100(t – age of diagnosis of CKD) / t] – 50) and SES_{ij} is the socioeconomic status measured by family income and/or parental educational achievement (For more detail regarding the specification of Age please see section 8.2.1). Here b_4 is quantifies the shift of the regression line for a one percent increase in age since CKD diagnosis. The parameter b_5 quantifies the effect of a 1-unit increase socioeconomic status on the shift of the regression line. In this extended model, the slope $b_1 + b_3$ estimates the effect of a decline of 5 ml/min|1.73m^2 of GFR, independent of age at diagnosis and socioeconomic status. To explore potential effect modification, the above extended model will be stratified by the presence of psychiatric diagnoses (e.g. ADHD).

In addition to general cognitive functioning as measured by IQ, the Neurocognitive Subcommittee is interested in exploring overall achievement, adaptive and social behavior, and measures of attention.

8.2.2 Left Ventricular Thickness

One key outcome for the cardiovascular aim is change in left ventricular (LV) thickness, as measured by echocardiogram at the visit 2 and every other year thereafter. LV thickness will be quantified as the LV mass index in units of g/m$^{2.7}$. We will also explore use of interventricular and posterior wall thicknesses, but constrain ourselves here to LV mass index. Due to the timing of the echocardiography, we will have approximately 300 children with two measurements of LV thickness during the 1st funding cycle: the analysis described below is restricted to these approximately 300 children.

Let Y_i be the 2-year change in LV thickness measured in units of g/m$^{2.7}$ for child i (= $y_{ij} – y_{ij-2}$). We will fit a regression model for the effect of decline in GFR on the change in LV thickness of the form $Y_i = b_0 + b_1t_i + b_2LV_i + b_3G_i$, where t_i measures the time between the two echocardiograms, centered at 2 years (= $(t_{ij} – t_{ij-2}) - 2$), the variable LV_i measures the baseline LV thickness, centered at its mean, and G_i is the decline of GFR in the year preceding the baseline LV measurement scaled to a 5-unit difference (= $(GFR_{ij-1} – GFR_{ij})/5$). This model will describe the average change in LV thickness as b_0 for those with 2 years between echocardiograms, average LV thickness at baseline, and no GFR decline. Individuals with 2-years between echocardiograms and average baseline LV thickness who exhibit a GFR decline of 5 ml/min|1.73m^2 will have an

average change in LV thickness of $b_0 + b_3$, such that b_3 quantifies the effect of GFR decline on change in LV thickness.

The above regression will be extended to control for possible confounding by age since diagnosis, blood pressure and body mass index by the addition of $+ b_4A_i + b_5SBP_i + b_6BMI_i$, where A_i is the percent of a child's age that the child has lived with CKD centered about 50% (= [100(t – age of diagnosis of CKD) / t] – 50), SBP_i is the average of two clinical systolic blood pressure measurements, and BMI_i is the child's body mass index. Here b_4 is quantifies the shift of the regression line for a one percent increase in age since CKD diagnosis. For example, in children 12 years of age, those who have had CKD since age 9 versus those who have had CKD since age 6 will differ in Y_{12} by $b_4[100x(6/12 – 3/12)]= 25b_4$. The parameters b_5 and b_6 quantify the effects of a 1-unit increase in systolic blood pressure and body mass index on the shift of the regression line, respectively. In this extended model, b_3 estimates the effect of a decline of 5 ml/min|1.73m^2 of GFR, adjusting for age at diagnosis, systolic blood pressure, and body mass index.

To explore potential effect modification, the above extended regression model will be stratified by the use of ACE inhibitors and/or quintiles of sodium intake, as measured with a food frequency questionnaire, to assess whether the effect of GFR decline on change in LV thickness differs in the presence of this therapy or salt intake.

Of course, more detailed analysis plans and further delineated analytic models will be possible as data accumulates and hypotheses develop. For instance, the Cardiovascular Subcommittee has expressed interest in the analysis of repeated measurements of clinical blood pressures as well as episodes of nocturnal 'dipping' blood pressure available from ambulatory blood pressure monitoring.

8.2.3 Linear Growth

Linear growth, as measured by height, is a central component of overall growth that is to be described in this cohort of children. Let Y_{ij} be the age- and gender-normed standard deviation score (SDS) based on the average of two heights measured in cm for child i at visit j, where visit j is taken at time t. The age- and gender-specific norms are derived as $Y_{ij} = (U_{ij} - \mu) / SD(\mu)$, where U_{ij} is the raw average of the two measured heights, μ is the age and gender specific mean norm height and $SD(\mu)$ is the standard deviation of μ; both μ and $SD(\mu)$ are based on tables provided by the National Center for Health Statistics.

A regression of the form $Y_{ij} = b_0 + b_1 t_{ij} + b_2 G_{ij} + b_3 G_{ij} t_{ij}$, where the variable G_{ij} is the decline of GFR in the preceding year scaled to a 5-unit difference (= $(GFR_{ij-1} - GFR_{ij})/5$), will describe the trajectory of linear growth as a line with intercepts b_0 for those with no GFR decline and $b_0 + b_2$ for those with a 5 ml/min|1.73m^2 decline in GFR, and slopes b_1 for individuals who have no GFR decline and $b_1 + b_3$ for those with a 5 ml/min|1.73m^2 decline in GFR. Here, the intercepts describe the initial difference in height SDS due to decline in GFR, and the slopes describe the linear rate of change in height SDS due to decline in GFR (For more detail about the specification of GFR please see section 8.2.2). As with IQ (see section 8.2.2), we will be able to investigate nonlinear growth rates by a polynomial expansion of t_{ij}, and the statistical dependence of repeated height measurements will be addressed using either mixed effects models or generalized estimating equations.

The above regression will be extended to control for possible confounding by age since diagnosis and caloric intake by the addition of $b_4 A_{ij}$ and $b_5 C_{ij}$, where A_{ij} is the percent of a child's age that the child has lived with CKD centered about 50% (= [100(t – age of diagnosis of CKD) / t] – 50) and C_{ij} is the caloric and/or protein intake measured by Food Frequency Questionnaire. Here b_4 quantifies the shift of the regression line for a one percent increase in age since CKD diagnosis. The parameter b_5 quantifies the effect of a 1-unit increase in caloric and/or protein intake on the shift of the regression line. In this extended model, the slope $b_1 + b_3$ estimates the effect of a decline of 5 ml/min|1.73m^2 of GFR, independent of age at diagnosis and caloric intake.

To explore potential effect modification, the above extended model will be stratified by the use of growth hormone and/or steroids to assess whether the effect of GFR decline differs in the presence of these therapies.

In addition to linear growth, we will explore changes in body mass and specific biomarkers, such as iPTH over the course of follow up.

9. POWER CALCULATION

9.1 Power Calculations for Cohort

The primary scientific goal of the study is to determine risk factors for rapid decline of GFR. For Cohort 1, the study enrolled 586 children. Of the 586 children, 129 had glomerular and 457 non-glomerular diagnoses. To date, the study has collected repeated GFR measurements to estimate the annual percent change in GFR (e.g., -10% will be indicative of a decline of 10% per year) for 99 children with glomerular and 409 children with non-glomerular diagnoses. Of these children, the subset at baseline with an iGFR above 45 ml/min/1.73m^2 was composed of 55 glomerular and 197 non-glomerular participants. For these subjects, Table 9.1 describes the urine protein creatinine ratio (uP/C) and GFR at baseline, and the annual percent and absolute change of GFR in ml/min|1.73m^2. Specifically, children with glomerular diagnoses, who had a uP/C above 0.5 (N= 32) experienced a median annual GFR decline of 10.8 ml/min|1.73m^2, which is steeper than the median annual decline of 4.3 ml/min|1.73m^2 observed for those with uP/C below 0.5 (n= 23). However, due to small sample sizes, the study has only 33% power to detect a significant difference between the percentages of children with glomerular diagnoses declining more than 10% per year (i.e., 35% and 56% among the 23 and 32 subjects with uP/C below and above 0.5, respectively). Similarly, in the non-glomerular group, those with a uP/C above 0.5 (N= 60) decline faster (-3.2 ml/min|1.73m^2) than those with uP/C below 0.5 (N= 137; -1.7 ml/min|1.73m^2). However, the study has only 51% power to detect a significant difference between the percentages of children with non-glomerular diagnoses declining more than 10% per year (i.e., 24% and 38% among the 137 and 60 subjects with uP/C below and above 0.5).

Table 9.1

	Glomerular		Non-glomerular	
N	**55**		**197**	
uP/C median	0.73		0.22	
IQR	0.28 to 1.37		0.12 to 0.63	
uP/C > 0.5	58%		30%	
	uP/C		**uP/C**	
	< =0.5	**> 0.5**	**< = 0.5**	**> 0.5**
N	23	32	137	60
Annual % decline greater than 10%	35%	56%	24%	38%
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Initial GFR (ml/min|1.73m^2)	57 (49, 70)	60 (50, 77)	58 (51, 68)	51 (48, 61)
% change per year	-7.8% (-12.0, -2.2)	-14.0% (-27.0, -0.1)	-2.9% (-9.2, 3.0)	-5.4% (-15.3, 2.9)
Absolute change per year (ml/min|1.73m^2)	-4.3 (-8.4, -1.2)	-10.8 (-15.9, 0.0)	-1.7 (-5.3, 1.8)	-3.2 (-8.7, 1.5)

To address these challenges, the study recruited an additional 305 children with early CKD (hereafter referred to as Cohort 2). Of the 305 children, 147 had glomerular and 158 non-glomerular diagnoses. It is expected that 90% and 85% of those recruited with glomerular and non-glomerular diagnoses will remain in the study, providing data for estimating GFR change, based on the current observed data in 55 glomerular and 197 non-glomerular subjects in Cohort 1 with a baseline eGFR > 45 ml/min/1.73m^2. Hence,

recruiting 147 children with a glomerular diagnoses and 158 children with a non-glomerular diagnoses will achieve a power of at least 70% to detect differential rates of GFR decline according to by uP/C strata (above or below 0.5) among those with an initial eGFR between 45 and 90 ml/min/1.73m^2.

Other potential biomarkers such as microalbuminuria will be explored. Preliminary data show that 75% of Cohort 1 has urine microalbumin > 30 mg/g creatinine. It is estimated that the presence of microalbuminuria in Cohort 2, which is a cohort of children with milder CKD will be lower (around 30 %). If 12.5% of the children with non-glomerular diagnoses, an eGFR from 45 to 90 ml/min/1.73m^2 and without microalbuminuria progress to renal failure during follow-up, the study will have 80% power to detect a risk ratio of 2.0 in children associated with microalbuminuria, with 90% confidence.

Additionally in the Cohort 2 children with glomerular diagnoses, investigators will have the ability to detect an increased risk of developing dyslipidemia associated with GFR decline >10% per year. If among children with glomerular diagnoses, 50% decline at > 10% per year, the study will have 80% power to detect an increased risk for the development of dyslipidemia associated with a risk ratio of 3.0 in those with a more rapid compared to those with a slower GFR decline (assuming a risk of dyslipidemia of 10% in those with slow GFR decline).

The CKiD study has contributed substantially to the knowledge of chronic kidney disease in children. However, even with the enrollment of Cohorts 1 and 2, gaps exist in the overall cohort as it stands. Enrollment of an additional cohort of 190 children with non-glomerular kidney disorders (Cohort 3) from early in their course of disease will facilitate characterization of the progression of CKD in this previously understudied population. Targeting children close to disease onset will enhance our ability to accomplish the aims of the CKiD study, respond to the needs identified to maximize the impact of research in the Kidney Research National Dialogue (KRND) initiative, and improve the long term outcomes for children with kidney disease. We based our sample size calculation on determining the size of the cohort that we will need to have p/2 precision if the true rate of a condition of interest (e.g., acidosis) is p. In other words, since the 95% confidence interval for p is $p \pm 1.96\sqrt{p(1-p)/n}$, the sample size n is determined by requiring $1.96\sqrt{p(1-p)/n}$ to be equal to p/2 (e.g., if p is 0.05, n will yield a 95% CI from 0.025 to 0.075). For p= 5%, 7.5% and 10%, the corresponding n's will be 292, 190 and 138, respectively. Although the desired sample size will be 292 in each group (i.e., to estimate 5% with $\pm$2.5% precision), this will amount to the recruitment in wave 3 of a cohort to be of the same size as the cohort recruited in wave 1 and will require longer than 2 years to recruit. Hence, we will recruit 190 children with a Non-Glomerular diagnoses.

9.2 Time-to-Event Analyses

We have presented power calculations for proposed investigations into the impact of GFR decline on disease outcomes using longitudinal analysis methods. Alternatively, analyses comparing the time to an event of interest will also be utilized, when appropriate, for outcomes such as ESRD. Table 9.2 shows the rate ratio thresholds that will be detectable with 80% statistical power at a 5% significance level according to three possible incidence rates among the unexposed (3, 6, and 9 events per 100 person-years) and by three levels of exposure prevalence (20%, 30% and 40%). Specifically, given an incidence of 6 per 100 person-years among the unexposed and 30% exposure prevalence we will have 80% power to detect a rate ratio of 1.85. However, if composite events were defined, such as in the AASK study, as (i) ESRD, (ii) a $\geq$ 50% decline in GFR, or (iii) a decline of at least 25 ml/min|1.73m^2, higher rates among the unexposed would be expected, resulting in greater statistical power.

Table 9.2

Detectable rate ratios with 80% power at 5% significance level

	Incidence among the unexposed:		
% exposed:	3 per 100 py *	6 per 100 py *	9 per 100 py *
20 %	2.52	2.00	1.79
30 %	2.28	1.85	1.68
40 %	2.19	1.79	1.63

* py = person-years

10. STUDY MANAGEMENT

10.1 Training

The DCC will assist and oversee the clinical coordinating centers to conduct training meetings for study investigators to review study design, consent procedures, patient recruitment and enrollment, data collection forms and schedules, test procedures and reporting. Study personnel from each of the clinical sites will be required to demonstrate proficiency in knowledge of the protocol for certification. Personnel will be complete an online knowledge assessment test and required to obtain a passing grade of 85%. All new coordinators who replace existing coordinators will be trained at their clinical sites and/or by their respective CCC. As such, the coordinators who review the DVDs will also be required to take the online knowledge assessment test and obtain a passing grade of 85%. Appendix D outlines the study timeline which includes training all participating clinical staff in the CKiD protocol, obtaining IRB approval from participating sites, etc.

Data management staff from the clinical coordinating centers will come to the DCC for training on the use of the web-based system. The web-based system is menu driven. New data management staff who replace staff trained at the DCC will be trained at their respective CCC. The DCC recommends data entry be performed by the sample person or people who are familiar with study forms.

10.2 Conference Calls and Site Visits

Over the course of the study, we plan to conduct conference calls with the principal investigators and coordinators to review recruitment and data quality. The DCC will also conduct site visits to each clinical coordinating center. We will conduct site visits for the purpose of observing operations, assessing adherence to protocols and certifying staff examination of procedures and interviews. It will also be an opportunity to obtain feedback regarding the protocol and their interaction with the DCC, clinical coordinating centers, the central laboratories and the repositories. This report will summarize findings as well as suggested changes for study-wide protocols.

10.3 Monitoring Study Conduct and Scientific Progress

10.3.1 Bi-monthly Steering Committee Conference Calls

The SC will meet by conference call bi-monthly, as arranged by the DCC. Bi-monthly conference calls will address issues of study conduct, including recruitment and retention, as well as scientific progress via review of concept sheets and draft manuscripts.

10.3.2 Semi-Annual Steering Committee and Annual Investigator/Coordinator Meetings
The SC and invited guests will meet in person two times per year. Additional meetings will be scheduled as needed during the recruitment and retention phases of CKiD. On an annual basis, a two day meeting will be held, and will roughly track the following agenda:

Day 1 (Steering Committee Meeting or Specific study procedure training)

8:30 – 12:00	Data report; study-wide subcommittees or procedural training (i.e., vascular testing)
12:00 – 1:00	Working lunch
1:00 – 5:00	Novel scientific presentations; subcommittee related to specific aims of CKiD

Day 2 (Investigator/Coordinator Meeting)

8:30 – 12:00	Scientific progress and priorities
12:00 – 3:00	Protocol Changes and Scientific Discussions

The data report will include sections on (1) recruitment and retention, (2) comprehensive summaries of data according to scientific aims of CKiD, (3) overall report on data quality, and (4) reports in regards to the central laboratories, central reading centers, and central repositories. The novel scientific presentations will include reports of proposed or accepted concept sheets and/or invited symposium on a specific scientific topic of interest. The protocol changes meeting will comprise discussions and decisions regarding alterations in the study protocol. Finally, scientific progress and priorities will assess the progress of every active concept sheet by roll call and rank order the CKiD scientific priorities over the subsequent six months, respectively.

10.4 Data Management and Reporting
10.4.1 Web-based data management system
The DCC has started and will continue to develop a web-based data management system (nicknamed Nephron). This system is built on extensible markup language (XML) technology, whereby every aspect of data forms (e.g., question text, possible responses, validation code) are stored in XML files [Gange 2000]. Like HTML, XML is tag-based, license-free, and platform- and vendor- independent. The XML files will function as a central repository from which all components of the data management system will be defined. Two main advantages of this approach are that (1) all components of the data system are guaranteed to be compatible, and (2) changes to the XML files are automatically translated throughout all components of the data management system.
The components developed from the central XML files include the database, data forms (online and hard-copies), codebooks, editing/queries, and reporting methods. We use the flexible, scalable and reliable MS SQL Server as our database storage system. Data fields are defined by the types, sizes and formats specified in the XML files. Our data entry forms are created in HTML. Hard-copy data forms and online data entry screens are identical (although hard-copy forms will divide the form with user-specified page breaks), thus enhancing the quality of the data entry. At the time of data entry, online data editing is accomplished using JavaScript code embedded in the HTML form

according to rules stored in the central XML files. These edit checks include field-level validations and within-form checks of logical consistency. Data transmission is done using MS data binding, which associates each data entry field on an HTML form with a corresponding field in a database table. The process of connecting the HTML forms with the database is done using remote data services, which is a subset of ActiveX data objects. After data is entered, additional central editing will be done to evaluate cross-form and longitudinal consistencies. Edit queries that are generated from these edits will be stored in tables accessible by remote data entry staff for resolution. A system for the generation of online reports will be developed to enable the clinical coordinating centers to explore the database.

The DCC is the central resource for compiling suggested changes to questionnaires and for developing and incorporating new questions for distribution to the clinical coordinating centers. As the protocol evolves and expands, the DCC staff develops data collection instruments. This ensures continuity of style and formatting across forms. Since instruments are centrally written and developed, changes and additions are juxtaposed with existing data collection methods and new questions are standardized with previously written questions. This enhances the flow of survey instruments and helps reduce respondent bias. Prior to the initiation of a new visit cycle (see diagram in section 5.4.1), data managers will create codebooks and input files to document variable names, questions and response codes. In previous multicenter studies coordinated by the DCC or CKiD, these codebooks have served as the resource for compilation and interpretation of the data collected. Investigators are encouraged to use the codebooks and refer to the data by the variable names to prevent miscommunication.

10.4.1.1 Security and Back-up

Nephron is protected using multiple layers of security. At the highest level, we utilize the Johns Hopkins University firewall that oversees access to all School of Public Health computers, have disabled ftp and telnet access to our dedicated study group server to prevent unauthorized access, and can implement IP-restrictions that control which computers can access Nephron. The web server on which Nephron is located has a secure 128-bit certificate, permitting us to use Secure Sockets Layer (SSL) encryption. This security ensures that all data (including usernames, passwords, and study data) are transmitted between browsers and web servers with maximum safety and prevents unauthorized personnel from gaining access to the data. We take advantage of Windows 2000 file system security whereby every user of Nephron, including staff at the clinical coordinating centers, has a managed user account on our servers with specific permissions and file access. Lastly, all fields changed by subsequent entry are recorded for tracking and to facilitate data recovery.

The Nephron database is automatically backed-up via a full copy to the Unix server disk on a daily basis. The entire system (including all users, Nephron SQL Server, and data files) is backed up daily using an 8mm AIT tape jukebox. The duplicated Nephron database will continue to be included in back-up script programs that automatically execute after each midnight. In addition to the daily automatic system backup of file systems, project specific data is also backed up to separate 8mm Exabyte tapes. On a

monthly basis, exact copies of the daily system backup tape and the project specific tapes are produced and stored off site in case of a local catastrophe. Backup and recovery are periodically tested.

10.4.1.2 Public data tape

To make the CKiD study data available to a wide range of external investigators and to respond to public requests for data, the DCC will assemble datasets for public use that will be archived and distributed by the NIDDK Data Repository, the Information Management Services (IMS). In July 2013, NIDDK established a public data sharing policy. The policy documents a suggested schedule regarding when study data should be provided to the data repository. KIDMAC has experience with creating public datasets and will de-identify the datasets to ensure that no linkages can be made with participants and that they are compliant with HIPAA regulations. The lack of identifiers between coded IDs included in the public data and coded IDs that exist in the study dataset ensures a high level of protection. The following are additional procedures used to ensure that no identification can be made: (1) recoding IDs with a randomly generated CASEIDs which are securely stored at the data center and not distributed or stored on the same medium as other study data; (2) eliminating any linkage to the clinical site and clinical coordinating center where a participant is followed; (3) removing the day and month values from baseline and birthdates; (4) converting all other dates into time durations from the participant's baseline date; and (5) eliminating all medical record, registry, and disenrollment data except year of death.

10.4.2 Quality Assurance

The DCC has experience with quality assurance and control initiatives undertaken throughout all aspects of cohort studies, including data management, clinic oversight, staff training and collaboration with central laboratories and national repositories. These experiences with quality assurance methods are summarized in five key areas.

First, the DCC will ensure quality at time of data collection. The DCC will spearhead the development of the manual of procedures, which is the heart of ensuring standardization across multiple sites. The DCC will coordinate the development of new data collection forms. Based on the DCC's experience with prior multicenter studies, we anticipate our overall residual error rate to be consonant with rates published from other multicenter cohort studies, on the order of 10 per 10,000 [Gibson 1994,Horbar 1995,Reynolds-Haertle 1992]. Second, the DCC will ensure quality at time of data entry. Our data management system has been designed with features to ensure quality data entry, including automatic field advance based on programmed skip patterns, range checks, and immediate edit reports for local resolution. Third, the DCC will ensure quality at time of data freeze. We will apply edit programs annually, updating the program in parallel with annual form and protocol changes. Fourth, the DCC will ensure quality at time of data summarization. Summary files are scientifically motivated files that summarize key study variables for the purpose of enhancing the management and standardization of data across various research initiatives. (see section 4.3.3 for more details.) Fifth and last, the DCC will ensure quality at time of data analysis. The DCC promotes the use of appropriate study designs and analytical methods to ensure quality interpretation and inference, which has included providing close collaborations and scientific partnership in analyses.

10.4.3 Summary Analytical Files

Data will be periodically frozen for construction of analytical data files, and the DCC distributes datasets to the clinical coordinating centers for use with local analyses that may occur concomitantly with central analyses ongoing at the DCC. To standardize the analysis of such complex data and reduce the likelihood of software coding errors, we will develop common summary data files, derived from the web-based database, for analyses. The final structure of these files would be determined in collaboration with the study investigators. These files will be distributed to investigators at the clinical coordinating centers so that specification of common variables for different scientific initiatives will be uniform. We foresee the need for the following files, although additional summary files may be created as the need arises.

First, VERT_DATEBASE is a vertical data file which will contain one record per person with the dates of each visit and the date of last contact. This file will contain the core data to assess follow-up rates and to determine who was seen at each visit defined by a specific calendar period. Second, KIDHIST will contain a record for each participant with key variables for describing the natural history of pediatric kidney disease. Interval encapsulating key events will be defined by dates last free of the event and when the event was first diagnosed. Such outcomes include: date of CKD diagnosis, initiation of treatment for CKD, first GFR < 15, first use of dialysis, transplantation and death. If the person has never had the event, then the date last free of the year of the event would be the date of last contact and the date first seen with the year of the event will be set to 2100, indicating a right-censored observation. If the date last free of event equals the date when the participant was seen with the event, then this is an uncensored observation. If the dates are different and the second date is less than 2100, this corresponds to an interval-censored observation. This file will be critical for implementation of survival analysis methods. Third, additional summary files (i.e., GFRSUMMARY, NEURO, CARDIO, ECHO, GROWTH, MEDSUM) will contain variables summarizing results from markers related to the scientific domains of CKiD (i.e., kidney, neurocognitive, cardiovascular, growth and medications) obtained at each visit. Thus these files will be vertical files with each record corresponding to one person-visit. These files will be critical for longitudinal analyses of these outcomes.

11. HUMAN SUBJECTS

11.1 Participant Consideration

This study is designed to determine the risk factors for decline in kidney function; the incidence of, and risk factors for, impaired neurocognitive development; risk factors for cardiovascular disease; and growth failure.

11.2 Clinical Feedback to Participants

The CKiD study investigators recognize the importance of reporting research information to the health care providers of participants. It is essential that investigators report clinically actionable information to the appropriate provider in a timely fashion. A procedure for reporting such information from the Data Coordinating Center to CKiD investigators will be implemented and described in the Manual of Procedures.

11.2.1 Transmission of Study Findings and Response Time

As results become available, they will be sent to participant's primary Nephrologist. Permission to forward this information will be obtained during the consent process at the time of study entry. Iohexol-GFR and estimated GFR, based on centrally measured serum creatinine, will be included in the report. Baseline results will be available on Nephron within a timely fashion and will include results of routine laboratory results obtained at the central laboratory. Similar reports will be provided on Nephron or via email to sites after the subsequent study visits. It is important to note that information from tests listed above may be less than the full complement received during tests performed for clinical evaluation.

Feedback from participants' cognitive and developmental assessments will be provided to the families of the participants by the local clinical psychologist in a timely fashion. A procedure for reporting such information is described in the Manual of Procedures.

11.2.2 Alert Findings

Participants and their primary Nephrologist will be immediately notified if potentially serious medical problems are identified during any of the examinations. Alerts will be defined as immediate or urgent.

11.2.2.1 Immediate Alerts

Immediate alerts are medical emergencies which are encountered or discovered at the time of the study visit such as hypertensive emergencies. These alerts will be evaluated by a physician who will determine the appropriate disposition. Immediate notification of the participant's primary Nephrologist should be accomplished by telephone, prior to the participant leaving the clinic. It is recommended that a follow-up letter documenting information discussed by phone should also be sent to the participant's primary Nephrologist.

11.2.2.2 Significantly Abnormal Results

In addition to centrally performed renal panels, clinical sites will perform a local Renal Panel for all study participants. Therefore for certain laboratory tests, such as potassium and glucose, sites will have documented local results; however, the central results will not be known immediately. Clinical sites will obtain central lab results from the Nephron website. On the website, certain significantly abnormal results will be noted with an asterisk. For these significantly abnormal results, it is recommended that the site coordinator notifies the primary Nephrologist within 24 hours after obtaining the results from the Nephron website or their local lab.

11.2.2.3 ECHO Alerts and ECHO Incidental Findings

ECHO Alert parameters include findings of congenital disease, vegetation, tumor, pericardial effusion and/or tamponade, left ventricular or atrial thrombus, or cardiomyopathy (hypertrophic/dilated). Local site should screen for “Alert” findings. The local sonographer will enter any of the “alert” findings which they identify during the examination on the Echocardiographic Sonographer’s Worksheet. In the event that an alert is found by the local sonographer, the sonographer should contact the site PI. The site PI should notify the study coordinator. The CKID study coordinator and/or PI will then be responsible for calling the patient’s referring physician (or physician on record) about the alert. Once the echo is received at the Cardiovascular Imaging Core Research Laboratory (CICRL), the images are also screened for alerts. In instances in which an “alert” parameter is identified and was not recorded on the site sonographer’s worksheet, the CICRL cardiologist will review the echo to confirm the alert and the CICRL will provide feedback to the site PI and clinical site sonographer. The site PI will then be responsible for contacting the Primary Nephrologist. All alerts will be reported on the website ECHO Report as “ALERT Found.” Otherwise, if no “alert” parameter is identified, then “No Alert” will be indicated on the ECHO Report. Incidental findings that do not fall under an “alert” parameter (such as a patent foramen ovale, or depressed LV function) will also be noted by the CICRL for baseline echos, and will be indicated on the feedback form provided by the CIRCL. It is up to the site coordinator to then notify the PI and referring physician.

11.3 Ethical Issues

The study will be conducted in accordance with Good Clinical Practice as contained in the U.S. Code of Federal Regulations governing the protection of human subjects (Title 21, Part 50) and the obligations of clinical investigators (Title 21, Part 312). This study will also be conducted in accordance with the Declaration of Helsinki.

11.3.1 Potential Risks (Study Related Adverse Events)

11.3.1.1 GFR

This study is considered to be of minimal to moderate risk because of the safety of the iohexol used for study related procedures. Iohexol (Omnipaque^{R}) is regularly used in Radiology for intravenous non-ionic contrast for CT studies of the abdomen/chest. The dose of iohexol in radiology is generally 50-200 cc; whereas we will use 5 for the GFR procedure. In a study of approximately 500 children in Scandinavia given iohexol to determine GFR [Stake 1991] using the same small dose specified in our study, iohexol did not cause side effects. In over 8000 studies recently reviewed by Nilsson-Ehle

[Nilsson-Ehle 2001] there were no side effects, even in subjects with a history of iodine hypersensitivity or adverse reactions to x-ray contrast investigations.

At 20 times the dose to be given in this study, iohexol has caused heart rhythm problems in about ½ of 1% of patients. As with any non-radioactive x-ray dye, there is a risk of allergic reaction. Symptoms of a possible allergic reaction include itching, rash, swelling of the face, tongue or throat, sneezing, nasal congestion, a sense of choking or other trouble breathing, wheezing, low blood pressure, dizziness and fainting. The use of iohexol would be contraindicated if a patient had a previous history of difficulty breathing after IV infusion of this agent. Allergic reactions will be treated with antihistamines, epinephrine, and steroids as needed. A study physician will be available during the time of the iohexol infusion.

11.3.1.2 Blood Draws
Drawing blood or inserting an IV catheter may cause faintness, inflammation of the vein, pain, bruising, infection or bleeding at the puncture site. The amount of blood drawn at each visit will not exceed the recommendations stated in TITLE 45—Public Welfare and Human Services Part 46—Protection of Human Subjects (i.e. the amount of blood to be collected may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.)

11.3.1.3 Neurocognitive Tests
Some questions may make a participant feel upset or uncomfortable. Participants will be informed that they do not have to answer any questions that make them feel severely upset or uncomfortable.

11.3.1.4 Echocardiogram
There are no confirmed biological effects on patients or instrument operators caused by exposures from present diagnostic ultrasound instruments (echocardiogram). Current data indicate that the benefits to patients of the prudent use of diagnostic ultrasound outweigh any possible risks that may be present.

11.3.1.5 Ambulatory Blood Pressure Monitoring
Possible risks associated with use of the ABPM include discomfort, bruising, or injury to the arm when the blood pressure cuff is inflated.

11.3.1.6 Vascular Tests
Skin redness or irritation from the heart monitor sticky pads is rare but may occur. Also removing these pads may cause some discomfort similar to taking off a band-aid.

11.3.1.7 Cardiac MRI
The magnetic fields and radio waves used during the MRI have not shown to cause any significant side effects. However, feelings of confinement (claustrophobia) and noise made by the magnet during the procedure may be bothersome. Also, because MRI uses powerful magnets, the presence of metal in the body may be a safety hazard. Prior to the exam, you will be asked to complete a standard questionnaire.

11.3.1.8 QardioArm (Home Blood Pressure) evice
Possible risks associated with use of the QardioArm device include discomfort, bruising, or injury to the arm when the blood pressure cuff is inflated.

11.3.1.9 Grip Strength
There are no confirmed side effects caused by using the grip strength instrument.

11.3.1.10 ActiGraph Physical Activity Monitor
There are no confirmed side effects caused by using the ActiGraph monitor.

11.3.1.11 Urine Collection Bag
Skin redness or irritation from the adhesive on the collection bag is rare but may occur.

11.3.2 Risk/Benefit Assessment
Having an accurate GFR measurement of the child may benefit their clinical care. Current estimations of kidney function from serum creatinine are quite inaccurate, as often as 50% of function can be lost before an increased serum creatinine is documented. A more accurate measure of GFR will allow more accurate assessment of risk for kidney disease progression, safer dosing of nephrotoxic drugs and other drugs cleared by the kidney. We will also be able to institute protective measures, such as more aggressive blood pressure control, at earlier stages of chronic kidney disease.

More complete information about cardiovascular and neurocognitive status will also benefit the clinical care of the child, as risk factors and deficits can be addressed through interventions.

11.3.3 Informed Consent
The consent process may differ somewhat by clinical site according to local IRB guidelines. The informed consent document will be structured such that it enables potential participants to indicate any aspect of the study with which they are not willing to be engaged. Separate consent forms will be provided for specific non-core tests or ancillary studies when appropriate. The informed consent will be available in Spanish and will cover all aspects of eligibility, risks and benefits of participation, confidentiality, withdrawal from the study, baseline testing and subsequent follow-up visits. Participants who turn 18 years old before the end of the study and have samples stored in the repositories will be re-consented per local IRB guidelines.

The Health Insurance Portability and Accountability Act (HIPAA) will affect the use or disclosure of protected health information in the CKiD study. Each clinical site may hold different requirements regarding HIPAA. Some institutions may request that this HIPAA language be inserted into the appropriate sections of the informed consent form; other clinical sites may require a stand alone document.

Consent must be obtained under circumstances that provide the prospective participant (if age appropriate) and parent or legal guardian sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue

influence. Participants must also meet the inclusion and exclusion criteria to be enrolled in the study.

The physician or designee will explain the study and the procedures at the clinical site and provide ample time to the child and the parents to consider joining the study. Each patient's legal guardian will provide written informed consent prior to any study procedures. Assent will be obtained from minors according to the age guidelines set by the clinical site's local IRB. Consent forms are either read to the subject or guardian or given to them to read with ample opportunity to ask questions or obtain further explanation. Consent forms will explain all procedures to be performed during the study. It will be made clear to the prospective subjects that their refusal to participate in the study will in no way jeopardize the quality of medical care they will receive nor will agreement to participate prevent them from withdrawing consent at a future time.

11.3.3.1 Alternative Methods of Consent

The continued follow-up protocol will be completed via phone, in-person or on-line to collect long-term outcome data on individuals who no longer complete regular CKiD study visits because they initiate renal replacement, become pregnant or are lost to regular follow-up (LTRFU). The LTRFU population are subjects who are no longer completing regular study visits at the site because they are unable to be reached, are chronic no shows (i.e., frequently miss scheduled visits), have transitioned to adult care and/or relocated to locations where they are unable to travel to a CKiD clinical site. Specifically, the LTRFU population is difficult to retain in the continued follow-up protocol because obtaining written consent presents a significant barrier when research staff are unable to speak with participants face to face. With the development of the web-based continued follow-up survey, an "on-line consent" process presents a viable alternative method to written informed consent. Website consent statements have been developed to serve as the "Letter of Information" for participants. In addition, sites can explore other methods consenting individuals such as a verbal consent process over the phone.

For this LTRFU population who are no longer being seen at the site, the research cannot practically be conducted without an alternative to written consent. To implement this method of consent, sites will need to do the following:

- Request a waiver of documentation of informed consent
- Request a waiver or alteration of HIPAA from their local IRB
- Specify the plan for consenting subject in the IRB submission

11.3.4 Confidentiality

Protection of participants depends on the joint activities of all clinical sites, the clinical coordinating centers, the repositories as well as the DCC. Extensive efforts will be made to ensure that participants' confidentiality is maintained. Each participant is assigned a unique study identification number and is never tracked through the study by name, social security number, medical record number, or other distinct personal identifiers. A log of the participant names, participant ID numbers, and pertinent registration information (e.g. home address, telephone number, social security number and emergency contact information) is maintained in a locked area at each clinical site. The

DCC, clinical coordinating centers and repositories do not have access to this log. Only the participant ID number (study ID) is given to the DCC, clinical coordinating centers and repositories; therefore, the study ID is the unique identifier for the data of a subject in the study's database. Any communication between the DCC, clinical coordinating centers and the repositories with the clinical sites regarding participant data will occur via the participant ID number. Any forms or documents sent to the DCC, clinical coordinating centers, repositories, IRB or Regulatory Authorities will have all personal identifying information removed. All research reports, articles, and presentations will report only aggregate findings.

A certificate of confidentiality will be obtained for the entire study from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify the participant, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the participant, except as explained below.

- The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).
- The Certificate of Confidentiality does not prevent the participant or a member of their family from voluntarily releasing information about themselves or their involvement in this research. If an insurer, employer, or other person obtains the participant's written consent to receive research information, then the researchers may not use the Certificate to withhold that information.
- The Certificate of Confidentiality does not prevent the researchers from disclosing information about intent to hurt themselves or others that is disclosed by the participant or a member of the participant's family.

11.3.5 Adverse Events

This study is not a clinical trial; therefore, documentation of adverse events will be obtained within 24 hours of a study procedure. Adverse events are considered any undesirable clinical experience (i.e., increased heart rate or blood pressure) occurring to a patient within 24 hours of a study procedure. However, if a participant has a serious adverse event (SAE) related to a study procedure (i.e., iohexol GFR) within 24 hours of the procedure, the event should be reported within specified local IRB time guidelines to the local IRB and the DCC. For the purposes of this study, a SAE within 24 hours of the study procedure will be considered any event that results in death, is immediately life threatening, requires inpatient hospitalization, or results in persistent or significant disability/incapacity. Life threatening means the patient is at immediate risk of death from the event as it occurred. All SAEs related to a study procedure will be reviewed monthly by the Steering Committee and annually by the External Advisory Committee. If the clinical site becomes aware of the death of a study participant between study visits, local IRB procedures should be followed and the DCC informed of the event within 5 days.

Appendix A: Steering Committee and Subcommittee Members List

Steering Committee

Susan Furth, MD, PhD (Voting Member)
Marva Moxey-Mims, MD, FAAP (Voting Member)
Alvaro Muñoz, PhD (Voting Member)
George Schwartz, MD (Voting Member)
Bradley Warady, MD (Voting Member)

Alison Abraham, PhD
Judith Jerry-Fluker, MPH
Joseph Flynn, MD
Arlene Gerson, PhD
Larry Greenbaum, MD, PhD
Lynne Haverkos, MD
Stephen Hooper, PhD
Frederick Kaskel, MD
Paula Maier, BA
Robert Mak, MD
Malot Minnick-Belarmino, PhD
Mark Mitsnefes, MD
Jacqueline Ndirangu, MPH
Christopher Pierce, MHS
Christine Smith, RN
Julia Starr, RN, MSN
Craig Wong, MD

Subcommittees related to specific aims:

Kidney Disease Progression

Susan Furth, MD, PhD (Co-Chair)
Robert Mak, MD, PhD (Co-Chair)
George Schwartz, MD (Co-Chair)

Alison Abraham, PhD
Meredith Atkinson, MD
Nadine Benador, MD
Tom Blydt-Hansen, MD
Donna Claes, MD
Larry Copelovitch, MD
Allison Dart, MD
Katherine Dell, MD
Vikas Dharnidika, MD
Sahar Fathallah, MD
Guillermo Hidalgo, MD
S. Paul Hmiel, MD, PhD
Judith Jerry-Fluker, MPH
Susan Massengill, MD
Tej Mattoo, MD, DCH, FRCP
Christopher Pierce, MHS
Alejandro Quirogo, MD
Dmitry Samsonsov, MD
Alice So, MD
Marty Turman, MD
Craig Wong, MD

Cardiovascular Outcomes

Mark Mitsnefes, MD (Co-Chair)
Joseph Flynn, MD, MS (Co-Chair)

John Barcia, MD
Gina-Marie Barletta, MD
Tammy Brady, MD
Kristin Burns, MD
Jeanne Charleston, RN
Christopher Cox, PhD
Janis Dionne, MD
John Jefferies, MD
Judith Jerry-Fluker, MPH
Deborah Jones, MD
Jonathan Kaltman, MD
Peace Madueme, MD
Juan Kupferman, MD
Hiren Patel, MD
Rulan Parekh, MD
Christopher Pierce, MHS
Anil Mongia, MD
Derek Ng, PhD
Alejandro Quirogo, MD
Jeffrey Saland, MD
Joshua Samuels, MD, PhD
Jack Weaver, MD
Amy Wilson, MD
Pamela Winterberg, MD
Ellen Woods, MD
Cynthia Wong, MD

Neurocognitive Outcomes

Stephen Hooper, PhD (Co-Chair)
Arlene Gerson, PhD (Co-Chair)
Bradley Warady, MD (Co-Chair)

Rebecca Johnson, PhD (Regional Psychologist)

Alison Abraham, PhD
Debbie Gipson, MD
Lyndsay Harshman, MD
Judith Jerry-Fluker, MPH
Amy Kogon, MD
Marc Lande, MD
Matthew Matheson, MS
Susan Mendley, MD
Bruce Morgenstern, MD
Victoria Norwood, MD
Shlomo Shinnar, MD
Joann Spinale, MD
Cynthia Wong, MD

Growth Outcomes

Frederick Kaskel, MD, PhD (Co-Chair)
Larry Greenbaum, MD, PhD (Co-Chair)

Alison Abraham, PhD
Amira Al-Uzri, MD
Ellen Brooks, PhD
Michelle Denburg, MD
Hilary Hotchkiss, MD
Judith Jerry-Fluker, MPH
Eunice John, MD
Juhi Kumar, MD, MPH
Craig Langman, MD
John Mahan, MD
Cynthia Pan, MD
Anthony Portale, MD
Poyyapakkam Srivaths, MD
Nancy Rodig, MD
Isidro Salusky, MD
Patricia Seo-Mayer, MD
Michael Schneider, MS
George Schwartz, MD
Shihtien Wang, MD
Bradley Warady, MD
Ora Yadin, MD

Appendix B: Study Proposal Form

Chronic Kidney Disease in Children Cohort Study
Concept Sheet
Submission Form

Please fill out all the lettered and numbered sections below

(*THIS FORM WILL NOT BE ACCEPTED UNLESS ALL OF THE FIELDS ARE COMPLETED*)

This form is intended for use for all collaborations. Where "☐" appears, double click on box and change default value from "not checked" to "checked".

A. GENERAL INFORMATION

1. Date of submission: **Click here to enter date.**
2. Lead investigator(s): **Click here to enter text.**
3. Study Title: **Click here to enter text.**
4. Contact Person (if different from lead investigator): **Click here to enter text.**
   a. Institution: **Click here to enter text.**
   b. Address: **Click here to enter text.**
   c. Telephone number: **Click here to enter text.**
   d. Fax Number: **Click here to enter text.**
   e. Email address: **Click here to enter text.**
5. Submission Type: ☐ Initial ☐ Revised [*Double click box to add check*]
   ☐ Addendum/Expansion of previously approved concept (Readme #___)
6. **Summary of Changes:** If submission is a revision (to a previously rejected) or an amendment (to a previously approved) existing concept sheet, please summarize all changes. (**NOTE:** In addition, please highlight or track all changes to the previously submitted concept sheet.)
7. Guideline (pages x – x) have been reviewed: ☐ Yes ☐ No

- By submitting this Concept, you agree to abide by the CKiD Publication Policy (https://statepi.jhsph.edu/ckid/investigator.html click on "Publication Policy"). The policy includes submitting manuscripts accepted for publications to NIHMS for PMCID number, if not using a NIH-approved PMC journal.
- Productivity (e.g., preliminary data analysis, presentation, and/or publication) of approved Concepts is required within 3 years of approval; otherwise the topic may be reassigned.

The completed CKiD Concept Sheet Submission Form should be sent electronically (either a Word or PDF) to Judith Jerry-Fluker at KIDMAC (jjerry@jhu.edu)

For Internal Use Only (DO NOT MOVE OR REMOVE)

Readme#: __ __ __ __ __ __ Processing: [ ] Expedited-Scientific [ ] Regular

B. CONCEPT INFORMATION

1. Please check the scientific subcommittee(s) that should review this concept sheet.
   [Double click box to add check.]

☐ Kidney Disease Progression ☐ Cardiovascular

☐ Neurocognitive ☐ Growth

2. Check whether the specific aims address core or non-core CKiD aims:

☐ Core CKiD specific aims
(proposal submitted on behalf of scientific subcommittee)

☐ Non-core CKiD specific aims/Ancillary

3. Topic (check all that apply):

☐ *CKD Progression*
☐ *CKD complications*
☐ *Cognitive Function*
☐ *Behavior*
☐ *Neuropsychology*
☐ *Drug Use*
☐ *Epidemiology*
☐ *Immunology*
☐ *Methodology*
☐ *Natural History*
☐ *Other:*

☐ *Cardiovascular Risk Factors*
☐ *Hypertension*
☐ *Lipids*
☐ *Inflammatory Markers*
☐ *Genetics*
☐ *Proteomics,*
☐ *Metabolics*
☐ *R01submission,*
☐ *Pharmacology*

4. Sites involved in the proposed study:
   ☐ All CKiD Sites
   ☐ Other, please list the clinical sites by name

_____
_____
_____
_____

5. Will this project require the withdrawal of specimens from the NIDDK DNA and/or Biological Samples Repository(ies)? ☐ Yes ☐ No

   a. If "Yes," the deadline date you will require specimens (MM/DD/YY): **Click here to enter date.**

   ▶ Following approval of the concept, you will need to obtain a fully executed Sample Data Use Certification (SDUC) between your institution and NIDDK. The information regarding how to obtain a SDUC will be sent to you or can be viewed on the CKiD website, under the "Investigator Resources" page.

6. CKiD Liaison: **Click here to enter text.**

   a. Institution: **Click here to enter text.**

   b. E-mail Address: **Click here to enter text.**

   c. FAX Number: **Click here to enter text.**

   d. Mailing Address: **Click here to enter text.**

7. KIDMAC Point Person: **Click here to enter text.**

Telephone Number: (410) 614-1277 or (410) 955-4320

FAX Number: (410) 955-7587

Mailing Address: Johns Hopkins University
Bloomberg School of Public Health
Department of Epidemiology
Room E7650
615 North Wolfe Street
Baltimore, MD 21205-1999

BEFORE SUBMISSION:

- ▶ Internal investigators should have the completed Concept Sheet (Concept) reviewed by another CKiD investigator
- ▶ External investigators should have the completed Concept reviewed by their co-investigator liaison (as indicated on page X of this form) from the studies to determine that this concept sheet is appropriate
- ▶ If no CKiD liaison exists, external investigator should contact Bradly Warady at bwarady@cmh.edu and/or Susan Furth at FurthS@CHOP.edu

C. STUDY DESIGN (2 – 3 pages)

Use the following organization to present your study plan and take whatever space is necessary to completely respond to each section. Complete in 12 point font only. Please submit electronic copies in WORD, RTF, or PDF format.

A. Lay Language Summary (*provide a one paragraph summary of the study and its impact on participants, written for a 10th grade reading level)*

Click here to enter text.

1. Does this project involve additional participant burden? (*Check all that apply*)
   - ☐ Additional specimen collection needed
   - ☐ New questionnaire
   - ☐ New procedure (i.e., x-ray, biopsy)
   - ☐ No additional specimens, questionnaires or procedures needed

B. BACKGROUND *(a brief description of the rationale for the sub study including references)*

Click here to enter text.

C. SPECIFIC AIMS AND HYPOTHESES *(Specimens and data provided by CKiD may only be used to complete the aims described in this concept. Additional testing and use of data, including transfer to another investigator, outside the scope of the stated aims and not explicitly stated in the concept are not allowed. Additional testing and data use require review and approval from the Steering Committee. In addition, upon approval of the proposed CS a Data Use Agreement form will be sent by the CKiD Data Coordinating Center (KIDMAC) and must be completed by the Lead Investigator.)*

Click here to enter text.

D. STUDY DESIGN (*summarize the type of study, inclusion criteria, and sample size)*

Click here to enter text.

E. SPECIFIC INCLUSION AND EXCLUSION CRITERIA

Click here to enter text.

F. LABORATORY METHODS *(Indicate the laboratory that will perform assays and if applicable, summarize how new studies will generate data, etc. If not applicable, check the N/A box.)*

Click here to enter text.

☐ N/A

G. QA/QC PROCEDURES *(for studies generating new laboratory data: summarize laboratory QA/QC procedures, participation in recognized program, past publication, etc., relevant to the proposed investigations or testing. If not applicable, check the N/A box.))*

Click here to enter text.

☐ N/A

H. STATISTICAL METHODS/ DATA ANALYSIS AND SAMPLE SIZE CALCULATIONS

(Include a statement about statistical power. Where appropriate, indicate which variables are needed from the CKiD database and anticipated support needed from CKiD. CKiD questionnaires with variables are available on line at https://statepi.jhsph.edu/ckid/. Include how data will be reported: on paper, what database, what file structure)

Click here to enter text.

Primary outcome variables:

Secondary outcome variables:

Other variables:

a. **Expected Visit Numbers:**

☐ N/A	☐ ALL visits		
☐ v1b (baseline)	☐ v2	☐ v3	☐ v4
☐ v5	☐ v6	☐ v7	☐ v8
☐ v9	☐ v10	☐ v11	☐ v12

b. DATA REQUESTED

Are you requesting a dataset to perform the analysis at your institution? ☐ Yes ☐ No

Please note that in order to receive CKiD data, a fully executed data use agreement must be obtained. The data use agreement is submitted after the concept sheet is approved by the Steering Committee. Please note that it may take at four (4) weeks or more to obtain a fully executed data use agreement.

I. PROPOSED TIMETABLE FOR STUDY COMPLETION:

Click here to enter text.

D. SAMPLE SPECIFICATIONS (tabular form)

Effective June 1, 2010, investigators requesting samples from the NIDDK Repository will have to agree to pay shipping costs before NIDDK will authorize the shipment of samples. The estimated ancillary shipping fees for samples are listed below.

Samples from the Biosample Repository at Fisher:

- Per box: Pulling/shipping up to 81 specimens - $101.45
- Per box: Pulling/aliquoting/shipping up to 81 specimens - $191.54

Samples from the Genetics Repository at Rutgers:

DNA from cell lines

- In vials (20 micrograms or less) - $25 per sample
- On plates, first plate - $20 per sample
- On plates, subsequent plates - $10 per sample

Primary DNA (from whole blood):

- In vials (5 micrograms or less) - $30 per sample
- On plates, first plate - $25 per sample
- On plates, subsequent plates - $1

1) Sample Type*: ☐ Serum ☐ Plasma ☐ DNA/Cells ☐ N/A
☐ Urine ☐ Hair ☐ Nails

*Specimens previously thawed for other initiatives will most likely be shipped. If unacceptable, give a reason below for requiring specimens not previously thawed

2) Sample Quantity**: Minimum: _____

Optimum: _____

**Please note that due to limited sample quantities stored at the NIDDK Repository, request for serum, plasma and urine should not exceed the following amounts:

- Serum no more than 0.1mL
- Plasma no more than 0.1mL
- Urine no more than 1.0mL

3) Expected Visit Numbers: ☐ N/A ☐ ALL visits
☐ v1b (baseline) ☐ v2 ☐ v3 ☐ v4
☐ v5 ☐ v6 ☐ v7 ☐ v8
☐ v9 ☐ v10 ☐ v11 ☐ v12

4) Expected Number of unique participants: _____

NOTE:
Upon Concept Sheet approval, a Repository Request Checklist (available on https://statepi.jhsph.edu/ckid/) must be submitted to Judith Jerry-Fluker via email at jjerry@jhu.edu or fax Judith Jerry-Fluker at 410-955-7587

E. STATEMENT OF AGREEMENT

I hereby acknowledge and agree that:

- All information that I provide in this Concept Sheet is complete and correct as submitted.
- Use of specimens and/or data is restricted to the aims outlined in Section C of the Study Design.
- IRB approval has been, or will be, obtained before any data and/or specimens are received.
- I will complete a CKiD Data Use Agreement, if this proposal receives approval and data is requested.
- Under no circumstances will I make the CKiD study subject 6 digit ID number public whether in documents or presentations, e.g., journal articles, abstracts, oral or poster presentations, or on any website.
- I will provide KIDMAC with a copy of all abstracts and/or manuscripts submitted, and notify KIDMAC when the abstract and/or manuscript is/are accepted.
- My signature below indicates a complete review, acceptance, and adherence to the guidelines for collaboration, publication, acknowledgment as outlined in this concept sheet submission form.

INSTRUCTIONS FOR SAVING CONCEPT SHEET:
After completing all of the sections, save the document in the following manner.

Lead Investigator's last name_title of concept sheet ***Example:*** Fluker_How to submit a concept sheet

Investigator Signature _____

Your signature indicates that you agree with all the above information and (if you are requesting data or specimens) that you have received local IRB approval or will attain approval before data or specimens are released.
NOTE: After your Concept Sheet has been submitted electronically, please sign and FAX this signature page and page one of the Concept Sheet to 410-955-7587 or email a scanned copy to Judith Jerry-Fluker (jjerry@jhu.edu).

F. ADDITIONAL SAMPLE AND DATA REQUIREMENTS

1. **For BIOLOGICAL SAMPLES ONLY:** A data file containing lab results and a codebook of specimen received must be submitted prior to the release of study visit data. NO EXCEPTIONS to this requirement.

2. Use of CKiD specimens require submission of a fully executed SDUC between investigator's institution and NIDDK.

3. Request for CKiD data require a fully executed data use agreement (DUA) between investigator's institution and Johns Hopkins University. Separate DUAs are required between all institutions with personnel who will have access to the data and Johns Hopkins University.

G. POTENTIAL FUNDING SOURCE

(pending application, planned application or funded effort)

Are you planning to submit an application for funding (i.e., R01, K23): ☐ Yes ☐ No
If yes, please specify:

Click here to enter text.

Note: Once funding is secured, lead investigator is responsible for notifying KIDMAC.

H. Internal Collaborations ONLY

1. NEW SUBSTUDIES (detail any anticipated additional participant and CKiD staff burden (in terms of amount of time required, additional visits, specimens to be collected, etc.))

Click here to enter text.

2. RELEVANCE (to overall CKiD aims and justification for use of CKiD specimens)

Click here to enter text.

3. CORE GOALS (Discussion of consistency with CKiD core goals and scope. Proponents of Concepts are encouraged to link with CKiD investigators to avoid overlap with ongoing initiatives. Please review the files listed at https://statepi.jhsph.edu/ckid/ to see active concept sheets by research topic in the CKiD.)

Click here to enter text.

Please read the Guidelines in the following Appendix ➔

Appendix C. Behavior Coding Mechanism (Reliability Codes for Each Task)

Below is the system to permit a rating for reliability of the data. By adding a second digit, we could capture the reason for why the reliability was compromised or a measure was not completed.

Primary codes:

1 Standard procedure, Reliable Results
2 Irregular Procedure, Reliability Affect Minor (e.g., child too tired)
3 Irregular Procedure, Unreliable (e.g., child too active, too ill; examiner errors)
4 Patient Attempted - Too Impaired to Complete
5 Patient Attempted - Examiner Discontinued
6 Patient Attempted - Refused to Finish
7 Patient Refused to Begin
8 Not attempted - Reason Unrelated to Patient (e.g., examiner forgot)

Secondary codes:

The second score would be after a decimal point (e.g., 1.0). It would indicate the reason why a measure was not completed or the reliability compromised.

.0 Not related to Physical Limitations (e.g., to be used with standard procedure with adequate reliability, or in situations where there was some problem that interfered with the assessment, but which was not directly related to the patient (e.g., trained examiner not available, improper test administration).

.1 Primarily related to physical limitations: Injuries or disabilities (not cognitive in nature) that necessitate nonstandard procedure.

.2 Primarily related to cognitive deficit: Impairments in cognition, behaviors that necessitate the use of nonstandard procedures, prevent completion of measure, or compromise reliability.

Appendix D. STUDY TIMELINE

JUNE 2004

June 21:	Conference Call for the CKiD Voting Members and Subcommittee Chairs to discuss the OSMB (formerly EAC) Report
June 22:	Conference Call for the Training and Education/Recruitment and Retention Subcommittee
June 24:	Conference Call for the Kidney Disease Progression Subcommittee
June 25:	Clinical Coordinating Centers Conference Call to Finalize Budget

JULY 2004

July 19:	Conference call with Steering Committee (SC) to discuss responses to the OSMB (formerly EAC) report
July 23:	Steering Committee Meeting
July 26:	Amended Protocol and letter sent to the OSMB (formerly EAC)
July 28:	Distribute MOP template to SC and Subcommittee Chairs
Late July:	Begin developing MOP

AUGUST 2004

Early Aug:	Develop MOP
Early Aug:	Distribute CKiD Protocol and IRB templates to sites to begin IRB process
Early Aug:	Distribute the CKiD Newsletter to site Principal Investigators and Coordinators
August 13:	Subcommittee Chairs and SC Members submit draft of MOP to KIDMAC
August 30:	IRB approval at Children's Mercy Hospital (CMH) and Johns Hopkins Hospital (JHH)

SEPTEMBER 2004 – OCTOBER 2004

Late Sept:	Pilot CKiD at CMH and JHH
Early Oct:	Refine protocol based on piloting CKiD at CMH and JHH
October 29:	ASN Meeting (St. Louis, MO)-CKiD Meeting for Principal Investigators and Coordinators

NOVEMBER 2004

Early Nov:	Training Meetings: Evidence of IRB submission prior to attending training
November 12:	Training Meeting (Baltimore)
November 19:	Training Meeting (Chicago)

DECEMBER 2004 – JANUARY 2005

Mid Dec:	Sites have IRB approval: 18 month Recruitment Period begins
January 1:	Begin Recruitment at CMH and JHU
Early January:	Development of Nephron (CKiD Web-based data management system)
Mid January:	Site visit to NIDDK Biosample Repository

FEBRUARY 2005 – MARCH 2005

Early Feb.:	Data for first CKiD participant entered into Nephron
February 10:	Site visit to Rutgers, DNA Repository
Early March:	Initiation of Midwest Clinical Coordinating Center One-On-One calls
Mid March:	Development of Nephron Enrollment Report
Late March:	Nephron Training for Clinical Coordinating Center personnel

APRIL 2005

April 1:	Begin Recruitment at participating sites. Total Recruitment=540 Recruitment milestone will be to recruit approximately 30 kids per month from all participating clinics for the 18 month recruitment period
Early April:	Finalized Visit 1a Central Biochemistry Laboratory kits
Early April:	Finalized and posted Visit 1a forms and QxQs.
Early April:	Finalized Visit 1a Code Books
Mid April:	Prepared Amendment I for IRB resubmission
Mid April:	Developed brochures and posters
Mid April:	Began development/taping of CKiD Study Training DVD
Late April:	Small Study Coordinator Training Meeting (New York)

MAY 2005 – JUNE 2005

Mid May:	Development of Nephron GFR Report
Mid June:	First East Coast Clinical Coordinating Center Conference Call
June 27:	First CKiD Visit 1b
Late June:	Development of Psychologist Corner on CKiD website

JULY 2005- AUGUST 2005

Late July:	Small Study Coordinator Training Meeting (Hawaii) Distribute CKiD Visit 1a Training DVD to Study Coordinators
Late July:	Developed Nephron Visit Control Sheet
Early August	First Concept Sheet Submitted
Mid August	First KIDMAC Report
Late August:	Small Study Coordinator Training Meeting (Baltimore)
Late August:	First Behavioral Training (Baltimore)

SEPTEMBER 2005 – OCTOBER 2005

September	Development of Nephron Quality Assurance Report
Late Sept:	Distribute Blood Pressure Manual and Training DVD to Study Coordinators
Early October	Creation of Coordinator's Corner on CKiD website
Mid Oct:	First Clinical Site ECHO Training

JANUARY 2006 – December 2006

Early January:	First CKiD Visit 2
Early March:	Development of Nephron Site Recruitment Report
Mid March:	Distribution of First Monthly Report on Expected and Past Due Visits and Data Completeness
Early April:	OSMB (formerly EAC) Approval of Amended CKiD Protocol
Late May:	First Full Day CKiD Meeting with Investigators and Coordinators

January 2007 – December 2007

Late April:	Full Day CKiD Meeting with Investigators and Coordinators
Late May:	CCC Data Entry Checks
Early Dec:	Submit CKiD II Renewal Application

MARCH 2008

Early March:	OSMB (formerly EAC) Meeting
Late February:	Close General Enrollment – continue recruiting African-American children
Late March:	Full Day CKiD Meeting with Investigators and Coordinators

2009

Early April:	Two-Day CKiD Meeting with Investigators and Coordinators
Late April:	Closed Enrollment of African-American
Late August:	Last baseline visit completed for Cohort 1

2010

Mid February:	East Coast Clinical Coordinating Center transferred from Johns Hopkins Medical Institutions to Children's Hospital of Philadelphia
Late April:	Two-Day CKiD Meeting with Investigators and Coordinators
Early May:	First child enrolled in phone/in-person follow-up protocol post CKiD
Early Nov:	IRB submission at Children's Mercy Hospital (CMH) and Children's Hospital of Philadelphia (CHOP)
Mid Nov:	Distribute the protocol and IRB template to begin the IRB submission process

2011

Early March:	Creation of CKiD Dossier
Mid April:	Two-Day CKiD Meeting with Investigators and Coordinators
Mid July:	OSMB (formerly EAC) Meeting

2012

Late January:	Participation in "Insights into CKD" workshop with CRIC investigators and NIDDK and Meeting with NIH External Expert Panel
Mid April:	Two-Day CKiD Meeting with Investigators and Coordinators. First meeting to include site psychologists.
Late May:	Closed Enrollment of Cohort 2 children with non-glomerular diagnosis
Late July:	OSMB (formerly EAC) Meeting
Late November:	Submit CKiD III Renewal Application

2013

Mid April:	Two-Day CKiD Meeting with Investigators and Coordinators
Late May:	Closed Enrollment of children with non-glomerular diagnosis
Early August:	OSMB Meeting
Mid August:	Deposited at IMS CKiD Cohort 1 Baseline Data
Early October:	Deposited at IMS CKiD data collected during first funding cycle

2014

January:	Deposited at IMS analytical data files
Late March:	Two-Day CKiD Meeting with Investigators and Coordinators
Early May:	Closed Enrollment of children with Cohort 2 glomerular diagnosis
Mid June:	OSMB Meeting

2015

Mid March:	Two-Day CKiD Meeting with Investigators and Coordinators
Early April:	Deposited at IMS CKiD data collected during second funding cycle
Mid May:	First Annual CKiD Workshop
Early July:	OSMB Meeting

2016

Mid March: Two-Day CKiD Meeting with Investigators and Coordinators
Late April: Second Annual CKiD Workshop
Late Sept: Began recruitment of non-glomerular children with less than 5 years CKD duration (Cohort 3)

2017

Late March: Two-Day CKiD Meeting with Investigators and Coordinators
Mid June: Third Annual CKiD Workshop
Early July: OSMB Meeting

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