

CKiD MANUAL OF PROCEDURES VERSION LIST as of 04/01/18

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**Chronic Kidney Disease in Children (CKiD) Study
MANUAL OF PROCEDURES**

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CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 1: STUDY PURPOSE

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 Eunice Kennedy Shriver 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.

1.1. CKiD 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.

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 progression, neurocognition, cardiovascular and growth. The protocol optimizes the power of the cohort design whereby levels and changes in the exposure of interest temporally precede outcomes.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY
SECTION 2: ORGANIZATIONAL STRUCTURE

2.1 CLINICAL SITES

The mid-west clinical coordinating center is directed by Dr. Bradley Warady (Principal Investigator [PI]) at the Children’s Mercy Kansas City in Kansas City, MO. The east-coast clinical coordinating center is directed by Dr. Susan Furth (PI) at the 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. The 50 clinical centers identified as potential CKiD study sites are listed in Table 2.1, Table 2.2 and geographically shown in Figure 2.1.

Table 2.1

CHILDREN’S MERCY HOSPITAL	PRINCIPAL INVESTIGATORS
Sites	
Arizona Kidney Disease and Hypertension Center	Gina Marie Barletta, MD*
British Columbia Children’s Hospital	Tom Blydt-Hansen, MD, FRCPC*
Egleston Children’s Hospital, Emory University	Larry Greenbaum, MD, PhD*
Cincinnati Children’s Hospital Medical Center	Donna Claes, MD*; Mark Mitsnefes, MD;
Seattle Children’s Hospital	Joseph Flynn, MD*
Children’s Hospital of Alabama	Sahar Fathallah, MD*
Boston Children’s Hospital	Nancy Rodig, MD*
Children’s Hospital of Winnipeg	Allison Dart, MD, MSc, FRCPC*
Children’s Mercy Kansas City	Bradley Warady, MD*
Medical College of Wisconsin	Cynthia Pan, MD*
University of Oklahoma Health Sciences Center	Anjali Nayak, MD*
Oregon Health and Science University	Amira Al-Uzri, MD*; Kelsey Richardson, MD
Phoenix Children’s Hospital	Martin Turman, MD, PhD*
Case Western Reserve University	Katherine Dell, MD*
St. Louis Children’s Hospital	Thomas Keefe Davis, MD*
Stanford University Medical Center	Cynthia Wong, MD*; Steve Alexander, MD
UCSF Children’s Hospital	Elaine Ku, MD, MAS*
University of California – Los Angeles	Isidro Salusky, MD; Ora Yadin, MD*
University of California – San Diego	Elizabeth Ingulli, MD*; Robert Mak, MD, PhD
University of New Mexico Children’s Hospital	Craig Wong, MD, MPH*
University of Texas Southwestern Medical Center	Mouin Seikaly, MD*
University of Wisconsin	Sharon Bartosh, MD*

*Clinical Site Principal Investigator

Table 2.2

CHILDREN'S HOSPITAL OF PHILADELPHIA	PRINCIPAL INVESTIGATORS
Sites	
Ann & Robert H. Lurie Children's Hospital of Chicago	Craig Langman, MD*
Carolina Medical Center	Susan Massengill, MD*
Children's Hospital of Philadelphia	Susan Furth, MD, PhD*
Children Hospital of Michigan	Tej Matoo, MD*
Children's Hospital at Dartmouth	Adam Weinstein, MD*
Children's Hospital at Montefiore	Frederick Kaskel, MD, PhD*
Children's National Medical Center	Larry Patterson, MD*
DeVos Children's Hospital at Spectrum	Alejandro Quiroga, MD*
East Carolina University	Guillermo Hidalgo, MD*
Hospital for Sick Children (Sick Kids)	Rulan Parekh, MD*; Lisa Robinson, MD
INOVA Fairfax Hospital for Children	Patricia Seo-Mayer, MD*
Johns Hopkins Children's Center	Meredith Atkinson, MD*
Indiana University, Riley Hospital for Children	Amy Wilson, MD*
Icahn School of Medicine at Mount Sinai	Jeffrey Saland, MD*
Loma Linda University	Cheryl Sanchez-Kazi, MD*
Nationwide Children's Hospital, Ohio State University	Amy Kogon, MD*
RBHS-Robert Wood Johnson Medical School	Joann Carlson, MD*
State University of New York, Downstate Medical Center	Anil Mongia, MD*
Texas Children's Hospital	Poyyapakkam Srivaths, MD*
University of Illinois at Chicago	Eunice John, MD*
University of Iowa	Jason Misurac, MD*
University of Kentucky	Stefan Kiessling, MD*
University of Michigan, Mott Hospital	Dave Selewski, MD*
University of Rochester Medical Center, Goliano Children's Hospital at Strong	Marc Lande, MD*; George Schwartz, MD
University of Texas, Houston	Joshua Samuels, MD*
University of Virginia	Victoria Norwood, MD*

*Clinical Site Principal Investigator

Figure 2.1



2.1.1 CHILDREN'S MERCY HOSPITAL

- Principal Investigator, Bradley Warady, MD
- Project Director, Julia Starr, RN, MSN, CNN, CCRP
- Study Coordinators, Sarah Smiley, RN, BSN, CCRC, Christine Smith, RN, BSN, CCRC
- Research Assistant, Leah Haddadi, BA
- Data Coordinator, Carolyn Worten

2.1.2 CHILDREN'S HOSPITAL OF PHILADELPHIA

- Principal Investigator, Susan Furth, MD, PhD
- Project Director, Jacqueline Ndirangu, MPH
- Research Program Manager, Maria Loudes Minnick, PhD
- Study Coordinators, Maleka Smith, BS, Natalie Walker, MSW, LSW
- Data Coordinator, Shumei Shang, MS

2.2 CKiD DATA MANAGEMENT AND ANALYSIS CENTER (KIDMAC)

Johns Hopkins University, Bloomberg School of Hygiene and Public Health

- Principal Investigator, Alvaro Muñoz, PhD
- Project Director, Judith Jerry-Fluker, MPH
- Research Data Analyst, Lynn Pereira, BS
- Administrative Coordinator/Research Assistant, Lucy Mulqueen, BS

2.3 NIH INSTITUTES

- NIDDK – Program Officer, Ziya Kirkali, MD
- NIDDK – Project Scientist, Susan Mendley, MD
- NICHD – Program Officer, Perdita Taylor-Zapata, MD
- NHLBI – Program Officer, Kristin Burns, MD

2.4 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 Susan Mendley, 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.

2.5 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), Jeffrey R. Botkin, Aviva Goldberg, Blanche Chavers, Avital Cnaan, Jami Levine and Mark Schluchter.

2.6 ADMINISTRATIVE WORKING GROUPS

Working groups were developed to provide expert input to the CKiD SC on specific areas of form and protocol development. The following working groups have been developed:

- Data Management and Quality Control Subcommittee; Alvaro Muñoz, Craig Wong (co-chairs)
- Laboratory/Specimen Working Group; George Schwartz (chair)
- Training and Education and Recruitment and Retention Subcommittee; Judith Jerry-Fluker (chair)

2.7 SUBCOMMITTEE RELATED TO SPECIFIC AIMS

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, protocols and the manual of procedures, guide CKiD in making optimal use of its data and specimens, and plan and attend annual CKiD meetings. Finally, each subcommittee will advise the SC on the merit of submitted CKiD concept sheets, as needed (see section 22). Specific tasks of the subcommittees are listed below and a list of subcommittee members is shown at the end of this section.

Each scientific area-based (SAB) subcommittee will participate in monthly conference calls for a focused discussion regarding project needs and/or operational issues (e.g., form or protocol revisions) specific to that individual subcommittee. These topics will also be discussed by SAB subcommittee members either via e-mail or by posting to their respective bulletin boards on the CKiD web site. However, if there are issues that cannot be resolved via e-mail or the bulletin board, supplementary conference calls may be requested in addition to the monthly conference calls on an as-needed basis.

If a group needs to discuss a paper or concept collectively, they can request a conference call by emailing the KIDMAC Project Director (jjerry@jhu.edu). There are 6 calls available each month for science. The first 6 requests that have been given scientific merit by the SAB will be approved by the KIDMAC Project

Director. If a group wishes to review a manuscript or PowerPoint presentation, the author should email the file to the KIDMAC Project Director. It will be posted to the group's discussion board for simultaneous viewing by investigators on a call.

A list of action items resulting from each call must be created and distributed to call participants. Additionally, a copy should be submitted to KIDMAC for posting to the CKiD web site. Groups that do not submit a list of action items may be denied future conference calls. Each request should contain the following information: 1) who will host the call (generally this will be an SAB subcommittee chair; 2) a list of participants; 3) date and time of call; and 4) reason for requesting the call. Requests may be reviewed by the CKiD Steering Committee and KIDMAC will be notified to set up a conference call only for approved requests. The SAB subcommittees are:

- Kidney Disease Progression; Susan Furth and George Schwartz (co-chairs)
- Neurocognitive Outcomes; Stephen Hooper and Rebecca Johnson (co-chairs)
Regional Psychologists; Stephen Hooper, Arlene Gerson, Rebecca Johnson
- Cardiovascular Outcomes; Joseph Flynn and Mark Mitsnefes (co-chairs)
- Growth Outcomes; Frederick Kaskel and Lawrence Greenbaum (co-chairs)

2.8 CKiD COMMUNICATIONS PROCEDURES

2.8.1 Resolving Inquiries Within CKiD Sites

The CKiD Manual of Procedures was designed to address most questions pertaining to protocols. There are times, however, when unusual or unpredictable situations arise, which may require further explanation than what is addressed in the procedures manual. Staff members at the CKiD sites are encouraged to bring their questions and concerns to their Site Study Coordinator (or the Site Study Coordinator designee).

When a question requires further clarification, the Study Coordinator should direct the question to KIDMAC. All inquiries should be addressed to the Project Director, Judith Jerry-Fluker. She can be contacted by phone 410.614-1277 or e-mail at jjerry@jhu.edu.

2.8.2 Communication Between KIDMAC and CKiD Sites

All project-related correspondence and communications between clinical sites and the data coordinating center are documented and filed at KIDMAC. KIDMAC uses two types of correspondence to document and communicate information to clinical site staff: a) numbered communication memos; and, b) site-specific memos. The numbering of memos will be continuous. (See distribution details below.)

If an inquiry pertains to an important matter involving all CKiD clinical site staff, then a *numbered communication memo* will be written and distributed study-wide. Any site-specific inquiries (not necessarily pertaining to all CKiD sites), which involve important protocol clarification issues, will be addressed via a *site-specific memo*.

- A. **Numbered Communication Memos.** These important memos are numbered to ensure that each one has been received and filed appropriately. If a memo is lost or misplaced, site staff should request another copy by contacting the KIDMAC Director or downloading that memo from the Administrative web site. Each numbered communication memo should be filed on-site in a Communication Memo Book, or filed electronically. The filed communication memos should be easily accessible to site staff for reference. KIDMAC distributes the numbered communication memos as follows:
- CKiD Steering Committee, Principal Investigators, Project Directors, SAB Chairs and Working Group Chairs

NOTE: It is the responsibility of the Clinical Coordinating Center Project Directors to ensure that other CKiD staff members in their respective consortium are given copies of the numbered communication memos (i.e., site coordinators, administrative staff, lab personnel, abstractionists and protocol-specific staff).

- B. **Site-Specific Memos** replying to a specific question or problem from one site staff member are distributed by KIDMAC to the staff member making the original inquiry. The staff member making the inquiry should share KIDMAC's response with other site staff, if appropriate.

2.8.3 Distribution of Study-Wide Correspondence and Materials

In addition to communication methods, which pertain specifically to field operations, KIDMAC has developed systems for distributing documents to the Steering Committee, the SAB subcommittees and Working Groups. In order to facilitate timely and efficient distribution, sites should inform KIDMAC of all staffing changes (i.e., name, title, address, phone, fax, e-mail address, etc) by posting a message to the Project Director's discussion board.

A. **Document Delivery System**

KIDMAC uses a document delivery system involving mainly first class US Mail, Priority Mail, FedEx and e-mail. The method used will depend on the time-sensitivity of the material and/or the recipient's preferred method of receipt.

B. **Internet – Website and Bulletin Boards**

- a) The CKiD website is used for the dissemination of information to both CKiD staff and the general public via restricted and unrestricted pages.

The address for the **unrestricted** page is <https://statepi.jhsph.edu/ckid/>. This page is accessible to the general public and includes links to:

- CKiD Specific Aims – outlines the specific aims of the study.
- CKiD Clinical Coordinating Centers – list the principal investigators and clinical coordinating centers affiliated with CKiD.
- CKiD Data Coordinating Center – list the DCC principal investigator.
- Central Laboratories – list the principal investigators at the central laboratories.
- Central Repositories – list the location of the data, biosample and genetic repositories.
- Sponsoring agencies – list of the NIH sponsoring agencies of CKiD.
- Internet links of potential interest –
 - Investigator Resources – links providing details information on submitting concept sheets, requesting samples, access to archived data and the CKiD publication policy.
 - The current version of the *Concept Sheet Submission Form* should be used for the submission of all concept sheets to KIDMAC. Concept sheets submitted on the wrong form will be returned to the author to be resubmitted on the correct form.
 - Publications and CKiD Dossier – a searchable database of all published CKiD manuscripts and a Microsoft PowerPoint presentation available for

viewing or downloading which describes the CKiD Study and is updated annually for CKiD meetings.

- Psychologist's Corner – link to an interactive form which generates feedback letters for the participant's nephrologist and parent(s), and young adult participants.
- Family Corner – links to a video about CKiD, newsletters and letters from the CKiD NIDDK Project Officer.

b) **Restricted** pages are also accessible from the main webpage:

<https://statepi.jhsph.edu/ckid/>; however, these pages are accessible only to CKiD staff with a valid password assigned by KIDMAC.

The restricted page contains links to study information useful to staff. A description of each section is as follows:

CKiD Study Administration Home Page

The home page announces news bulletins and contains links to Study Administration, CKiD Communities, and Current Science.

- CKiD Staff Directory – The electronic version of the CKiD staff directory on this page receives regular updates. Additions or changes to the directory should be done by using the online form.
- Current Science – Discussion boards for concept sheets, manuscripts, and conference announcements/abstracts. The most current CKiD concept sheets, manuscripts, and conference abstracts are posted to these boards. All CKiD staff are welcome to participate in the review process and post comments. The boards also serve as a searchable archive of CKiD science.
- Study Documentation – This section provides links to the following CKiD administrative forms:
 - Current and past Protocol Amendments and supporting documents
 - All CKiD communication memos distributed by KIDMAC by year
 - Current and past *Manual of Procedures*
 - An excel spreadsheet detailing all CKiD forms and the current version that should be used.
 - Changes and revisions to forms and protocols for upcoming visits are posted on the appropriate discussion board. The boards can be accessed here. ALL comments concerning form changes, proposals for new protocols or initiatives, and proposed changes to the lab protocol for a particular visit number should be posted on the discussion board. Prior to the start of a new year, the SC and/or appropriate subgroups will review all comments posted and decide which will be implemented for during the form change cycle.
- CKiD Discussion Boards – The CKiD is made up of many different groups of people. This page lists the most prominent groups and links to their own individual discussion board. Currently, only a few CKiD Communities have pages however KIDMAC can write additional pages. CKiD staff that would like to request, change, or update a page should contact the KIDMAC Project Director, jjerry@jhu.edu.

- Steering Committee – SC members will find pertinent links to review their meeting and call minutes, news and deliverable updates.
- Scientific Area-Based Subcommittee – The subcommittees, the chairs of the subcommittee, and any relevant announcements are listed. These message boards are typically used to post agendas and minutes for Subcommittee conference calls and notices of interest to a particular group. In addition, abstracts and non-visit-specific proposals may be posted to these message boards for review by CKiD staff.
- Project Directors – The Project Directors do not have a discussion board of their own; however, they do have access to all of the other discussion boards.
- Laboratory and Specimen Group – The Lab Group does not have a discussion board but have access to all other discussion boards.
- Data Management, Analysts and Quality Control – Links to statistical and analytic resources for CKiD analysts.

CKiD Coordinator’s Corner Page

The “Coordinator’s Corner” webpage provides information to study coordinators on proper interviewing strategies, form completion, study updates, IRB documents, instructions for families, study-wide newsletters and links to Blood Pressure Certification training and feedback tools. Study coordinators are also able to request lab kits, dry ice shippers, ABPM monitors and Actigraph monitors by selecting the appropriate request form, and notify the appropriate CKiD personnel when data, specimen and/or devices are shipped. When an online form is completed, an email is generated and sent to the appropriate center (i.e., MW CCC, EC CCC, CBL, Repository or ABPM Lab). This online request process has helped the CCCs track study visits, lab kits, ABPM and Actigraph monitors.

For technical questions or problems regarding access to the CKiD website or to have a password assigned, contact Judith Jerry-Fluker (410) 614-1277 or jjerry@jhu.edu. Individuals are encouraged to post their own documents directly to the bulletin boards, with the exception of documents with charts and/or graphs. Documents to be posted should be e-mailed to Judith Jerry-Fluker at jjerry@jhu.edu.

Individual sites are encouraged to develop their own local websites. KIDMAC will provide a link to these sites. Maintenance and control of these local resources are the responsibility of local sites, not KIDMAC.

Steering Committee and Subcommittee Members List

Steering Committee

Susan Furth, MD, PhD (Voting Member) George Schwartz, MD (Voting Member)
Ziya Kirkali, MD, FAAP (Voting Member) Bradley Warady, MD (Voting Member)
Susan Mendley, MD (Voting Member)
Alvaro Muñoz, PhD (Voting Member)

Alison Abraham, PhD	Frederick Kaskel, MD	Joshua Samuels, MD
Kristen Burns, MD	Paula Maier, BA	Sarah Smiley, RN
Judith Jerry-Fluker, MPH	Robert Mak, MD	Christine Smith, RN
Joseph Flynn, MD	Malot Minnick-Belarmino, PhD	Maleka Smith, BS
Arlene Gerson, PhD	Mark Mitsnefes, MD	Julia Starr, RN, MSN
Larry Greenbaum, MD, PhD	Jacqueline Ndirangu, MPH	Perdita Taylor-Zapata, MD
Stephen Hooper, PhD	Derek Ng, PhD	Craig Wong, MD
Rebecca Johnson, PhD	Jeffrey Saland, MD	

Subcommittees related to specific aims:

Kidney Disease Progression

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

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

Neurocognitive Outcomes

Stephen Hooper, PhD (Co-Chair)
Rebecca Johnson, PhD (Co-Chair)
Arlene Gerson, PhD (Regional Psychologist)
Alison Abraham, PhD Bruce Morgenstern, MD
Debbie Gipson, MD Victoria Norwood, MD
Lyndsay Harshman, MD Shlomo Shinnar, MD
Judith Jerry-Fluker, MPH Joann Spinale, MD
Amy Kogon, MD Cynthia Wong, MD
Marc Lande, MD
Matthew Matheson, MS
Susan Mendley, MD

Cardiovascular Outcomes

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

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

Growth Outcomes

Frederick Kaskel, MD, PhD (Co-Chair)
Larry Greenbaum, MD, PhD (Co-Chair)
Alison Abraham, PhD Anthony Portale, MD
Amira Al-Uzri, MD Nancy Rodig, MD
Ellen Brooks, PhD Isidro Salusky, MD
Michelle Denburg, MD Michael Schneider, MS
Hilary Hotchkiss, MD George Schwartz, MD
Judith Jerry-Fluker, MPH Shihtien Wang, MD
Eunice John, MD Bradley Warady, MD
Juhi Kumar, MD, MPH Ora Yadin, MD
Craig Langman, MD
John Mahan, MD

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 3: CLINICAL MANAGEMENT

3.1 RECOMMENDATIONS FOR SPACE

Office, storage and patient space will be different at each clinical site. Adequate space to see participants, to complete and store forms, to file or store participant records, and for private workspace for team members must be available. Thus, the goal is to have organized and efficient use of available space to facilitate successful implementation of the study.

Each clinical site will need space for the following:

3.1.1 Patient Care Space

Many clinical sites will have the use of an outpatient clinic, hospital facility, or General Clinical Research Center (GCRC). If possible, the patient care space should be easily accessible for participants, preferably near a parking facility and/or public transportation. Although one space to perform all the activities necessary for the study would be optimal, it may be necessary to have the patient care space in more than one location depending on the study activity and the availability (or limitation) of space within a particular institution. The environmental settings of the room where the patient care activities are performed should be considered. This place must be comfortable for the patient and free of distractions. For physical examinations and neurocognitive testing where sensitive information might be obtained, a private and quiet location must be considered. It would be ideal to have enough room in the patient care space to allow for the completion of forms and/or technical duties, while seeing participants. The location of this room should be convenient for handling biologic samples with access to the following: a centrifuge for spinning blood, a refrigerator and freezer to store blood and urine samples, a work table/counter with sink for handling and processing blood and urine samples. If possible, the patient care space should allow for storage of needed study materials such as laboratory supplies and files for data forms. For some institutions, it may be necessary to consider a patient care space that is in reasonable proximity to the pharmacy since Iohexol used for the GFR testing may be stored in the pharmacy.

3.1.2 Office Space

Adequate space should be available for team members to conduct their work when they are not with study participants. Privacy for phone calls with study participants and for participant conferences are essential. A room to conduct study team meetings should be available. A copy machine and computer should be nearby. Space for a CKiD staff member to monitor the quality of data collected should be available.

3.1.3 Storage Space

Storage space must be available for participant records, data collection forms, medications, and office and laboratory supplies. A cabinet that can be locked should be convenient to store medication and participant records. Data collection forms may also be stored electronically per individual site regulations.

3.2 RECOMMENDATIONS FOR SUPPLIES/EQUIPMENT

The Study Coordinator or designated person will be responsible for requesting and maintaining an inventory of supplies sent from the central facilities and those purchased or obtained locally. Supplies will include office and laboratory supplies as well as data forms.

3.2.1 Office Supplies/Equipment

Office supplies such as photocopy/printer paper, pens, pencils, water proof markers, staples, labels, notebooks, dividers, file folders and computer maintenance supplies, etc. should be readily available.

A computer with access to medical information such as lab results and Discharge Summaries of study participants is useful.

3.2.2 Laboratory Supplies/Equipment

Supplies for laboratory functions, processing, handling and shipping should include items from the following list that is comprehensive but not inclusive: urine collection equipment for participants (jug or other collection containers); venous access supplies (vacutainer needles and holders, butterfly needles, IV catheters, leur locks or heparin lock, normal saline flush and/or heparin flush, tourniquets, rubber gloves, 3 and 10 or 12 mL syringes; gauze, cotton balls, band aids, alcohol wipes, tape, armboards); lab processing supplies (serum separator tubes (SST), EDTA tubes, pipettes, biohazard garbage liners, sharps disposables); shipping supplies (urine mailing tubes, serum mailing tubes, routine urinalysis conical tubes, Fed Ex pouches, ziplock plastic bags, mailing box and styrofoam insert, dry ice).

3.2.3 Blood Pressure Equipment

Each clinical site will be given an aneroid BP machine to be used on all study participants. A chair with back support should be used by participants when their blood pressure is being examined.

Each clinical site will use a SpaceLabs™ 90217 ABPM for the Ambulatory Blood Pressure Measurement. The SpaceLabs™ 90217 ABPM will be provided to clinical sites on an as needed basis. The site coordinator will request the SpaceLabs™ 90217 ABPM when needed via the CKiD website.

3.3 SCHEDULING OF ACTIVITIES

A system and an organization that will facilitate the orderly and efficient management of multiple activities including administrative, patient care, data management and quality control must be developed. The Study Coordinator will be in charge of these activities but has the authority to delegate when appropriate to team members.

3.3.1 Administrative Activities

These activities include: 1) securing adequate space, equipment and supplies for study needs; 2) developing a working relationship with liaison personnel: the pharmacist, clinic and/or GCRC non-study staff, personnel from echocardiography, psychology and radiology, local laboratory, medical records, participant registration, and billing/accounting; 3) ordering and maintaining a supply and the storage of Iohexol; 4) communicating with referring physicians about participant test results and updates; 5) coordinating study activities with consortium institutions, if appropriate; 6) scheduling clinic appointments that are compatible with the participants, staff schedules, and clinic/GCRC schedules and available space; and 7) arranging for reimbursement for parking and transportation.

Because of the varied activities necessary to conduct CKiD, it is necessary to coordinate activities among the liaison personnel as listed above. Forming an alliance with liaison personnel is critical to the success of the study. Therefore, liaison personnel should be provided information about the importance of the study, the goals of CKiD, and the procedures pertinent to their role in the study.

The Study Coordinator will notify team members of CKiD activities and facilitate study related communication and problem solving. Team meetings should be scheduled when needed. The Study Coordinator will be responsible for ensuring that Protocols, Manuals of Procedures, and data forms are current. Every effort should be made to create a clinic setting in which workspace, workloads and communication will facilitate conducting the study as efficiently and effectively as possible.

3.3.2 Scheduling Participant Visits

During all phases of the study, special emphasis should be placed on adhering to the participant's target visit window. Participants should be scheduled, if possible, at their convenience but also at a time that is compatible with team and other clinic/GCRC activities. Phone calls and/or reminder cards are encouraged to promote adherence to appointments. In order to provide flexibility when scheduling study visits, each study visit may be scheduled during varying time periods. Specifically, V1a should be scheduled as soon as possible 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 (\pm one month) after V1a or no more than fourteen (14) years after V1a for visits that are difficult to schedule.
- If the ECHO, Vascular Testing, Ambulatory Blood Pressure Monitoring (ABPM), cardiac MRI and Neurocognitive testing data cannot be obtained during the child's scheduled study visit, these

measurements will 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 Testing, cardiac MRI or Neurocognitive testing within one month of the scheduled visit, the site should contact their respective CCC for further instructions.

When visits are missed, rescheduling as soon as possible for an appointment within the window should be attempted. 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.

3.3.3 Quality Data Collection

To ensure that CKiD has quality data, team members must know the purpose of the study, the protocol design and the sections of the Manual of Procedures (MOP) that are pertinent to their roles in the study. When appropriate, liaison personnel will be notified of the scheduled study visit and appraised of the necessary procedures from the MOP. If protocol expectations and study goals are clear and common to all team members, then protocol adherence by staff will help ensure quality data collection and a pleasant working environment. Prior to each CKiD visit, appropriate forms will be assembled, labeled, and distributed to designated personnel. The Study Coordinator will review all data forms for completeness and accuracy. Also, the study coordinator will make electronic or hard copies of all data forms and ensure timely submission of the original data to the Clinical Coordinating Center and the Data Coordinating Center, if appropriate. Data forms will be filed in an area convenient for study personnel's access. The Study Coordinator and technical personnel will coordinate an effort to mail the blood and urine samples of CKiD to ensure prompt shipment to the Central Labs. The Study Coordinator or designated person from each clinical site will monitor and ensure the calibration of blood pressure equipment. A CKiD staff member from the Clinical Coordinating Center associated with a specific clinical site may visit a site and will hold quarterly conference calls for the purpose of monitoring the quality of data collection.

3.4 CKiD REFERENCE MATERIALS

3.4.1 Reference Materials

Each site should maintain electronic or hard copies of the Protocol, Manual of Procedures and CKiD Address Directory.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 4: STUDY DESIGN

4.1 STUDY DESIGN

The design of the CKiD study is a prospective, observational cohort of children with chronic kidney disease (CKD). 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 primary outcomes. Exposures will be measured at baseline and scheduled annual follow-up visits will permit the subsequent updating of the exposures in cohort participants. The objective of annual follow-up visits will be to collect information on exposures and outcomes; measure kidney disease progression; assess cardiovascular disease risk factors, neurocognitive impairment and growth failure and other co-morbid conditions; determine health care utilization patterns; and assess the occurrence of clinical events related to primary outcomes since last contact. All exposures and markers of disease progression will be measured using standardized procedures. 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 CKD.

The structure of the contact pattern has been dictated by the scientific aims of the study. Table 4.1 depicts the contact pattern and the corresponding information to be obtained at baseline and at each annual follow-up visit. Specifically, the baseline visit will be comprised of two separate visits within the first year. The first component of the baseline visit (V1a) will occur during the child's initial visit to the clinic which will include procedures to obtain a 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. For children over the age of 3 years old, Visit 1b will occur within 6 months. The one to six month lag between V1a and V1b is necessary because in a subcohort of participants the procedures needed to measure the GFR do not provide an environment conducive to an unbiased assessment of some of the neurocognitive tests.

Correct measurement of baseline parameters is of the utmost importance to the success of this study because it is the foundation against which CKiD will determine all study outcomes. In addition the attention to detail in the collection and recording of the baseline data sets the tone for the conduct of the study throughout the entire period. It is essential that the procedures described in the [Manual of Procedures](#) for collecting and recording baseline parameters be followed exactly. Precision is essential for valid comparisons of future exposures within the cohort across time.

Table 4.1 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 tests.

^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 Strength:** Grip strength will be measured in participants 6 years old and older.

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/1.73m² 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, the Cohort 2 was comprised 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.

The tables below show the ranges of S_{Cr} that correspond to a GFR between 30 and 90 ml/min/1.73m² for children of different genders and heights that were recruited in Cohort 1. The lower serum creatinine limit of the range corresponds to an estimated GFR of 90 ml/min/1.73m² and the higher limit corresponds to an estimated GFR of 30 ml/min/1.73m². Two serum creatinine measurements must be obtained for all children. Both measurements must also fall within the serum creatinine range that corresponds to a GFR between 30 and 90 ml/min/1.73m² in order for the child to be eligible for enrollment in CKiD. The first measurement must be within the past six months and the second measurement within the past 18 months.

The S_{Cr} measurements are based on the estimated Schwartz GFR measurement (eGFR=kL/S_{Cr}).

- In Table A, **k = 0.45** for males and females between 12 months and 18 months.
- In Table B, **k = 0.55** for males between 19 months and 13 years old (before 13th birthday); and females 19 months and older.
- In Table C, **k = 0.70** for males after 13th birthday.

Table 4.2a, 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/1.73m² **before 19 months old

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)]

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.

Table 4.2b, 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/1.73m²

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} = 0.8 (ineligible)]

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.

Table 4.2c, MALES after 13th birthday

Height		SCr			Height		SCr			Height		SCr		
(cm)	(in)	Low	-	High	(cm)	(in)	Low	-	High	(cm)	(in)	Low	-	High
100	39.4	0.78	-	2.33	134	52.8	1.04	-	3.12	167	65.7	1.30	-	3.89
101	39.8	0.79	-	2.35	135	53.0	1.05	-	3.15	168	66.0	1.30	-	3.92
102	40.2	0.79	-	2.38	136	53.5	1.06	-	3.17	169	66.5	1.31	-	3.94
103	40.6	0.80	-	2.40	137	54.0	1.07	-	3.19	170	67.0	1.32	-	3.96
104	41.0	0.81	-	2.42	138	54.3	1.07	-	3.22	171	67.3	1.33	-	3.99
105	41.3	0.82	-	2.45	139	54.7	1.08	-	3.24	172	67.7	1.34	-	4.01
106	41.7	0.82	-	2.47	140	55.0	1.09	-	3.26	173	68.0	1.34	-	4.03
107	42.0	0.83	-	2.49	141	55.5	1.10	-	3.29	174	68.5	1.35	-	4.06
108	42.5	0.84	-	2.52	142	56.0	1.11	-	3.31	175	69.0	1.36	-	4.08
109	43.0	0.85	-	2.54	143	56.3	1.11	-	3.33	176	69.3	1.37	-	4.10
110	43.3	0.86	-	2.56	144	56.7	1.12	-	3.36	177	69.7	1.38	-	4.13
111	43.7	0.86	-	2.59	145	57.0	1.13	-	3.38	178	70.0	1.38	-	4.15
112	44.0	0.87	-	2.61	146	57.5	1.14	-	3.40	179	70.5	1.39	-	4.17
113	44.5	0.88	-	2.63	147	58.0	1.15	-	3.43	180	70.9	1.40	-	4.20
114	45.0	0.89	-	2.66	148	58.3	1.15	-	3.45	181	71.3	1.41	-	4.22
115	45.3	0.89	-	2.68	149	58.7	1.16	-	3.47	182	71.7	1.42	-	4.24
116	45.7	0.90	-	2.70	150	59.0	1.17	-	3.50	183	72.0	1.42	-	4.27
117	46.0	0.91	-	2.73	151	59.4	1.17	-	3.52	184	72.4	1.43	-	4.29
118	46.5	0.92	-	2.75	152	60.0	1.19	-	3.54	185	72.8	1.44	-	4.31
119	47.0	0.93	-	2.77	153	60.2	1.19	-	3.57	186	73.2	1.45	-	4.34
120	47.2	0.93	-	2.80	154	60.6	1.20	-	3.59	187	73.6	1.45	-	4.36
121	47.6	0.94	-	2.82	155	61.0	1.21	-	3.61	188	74.0	1.46	-	4.38
122	48.0	0.95	-	2.84	156	61.4	1.21	-	3.64	189	74.4	1.47	-	4.41
123	48.4	0.96	-	2.87	157	62.0	1.22	-	3.66	190	74.8	1.48	-	4.43
124	49.0	0.97	-	2.89	158	62.2	1.23	-	3.68	191	75.2	1.49	-	4.45
125	49.2	0.97	-	2.91	159	62.6	1.24	-	3.71	192	75.6	1.49	-	4.48
126	49.6	0.98	-	2.94	160	63.0	1.24	-	3.73	193	76.0	1.50	-	4.50
127	50.0	0.99	-	2.96	161	63.4	1.25	-	3.75	194	76.4	1.51	-	4.52
128	50.4	1.00	-	2.98	162	63.8	1.26	-	3.78	195	76.8	1.52	-	4.55
129	50.8	1.00	-	3.01	163	64.0	1.26	-	3.80	196	77.2	1.52	-	4.57
130	51.0	1.01	-	3.03	164	64.6	1.28	-	3.82	197	77.6	1.53	-	4.59
131	51.6	1.02	-	3.05	165	65.0	1.28	-	3.85	198	78.0	1.54	-	4.62
132	52.0	1.03	-	3.08	166	65.4	1.29	-	3.87	199	78.3	1.55	-	4.64
133	52.4	1.03	-	3.10										

*Serum Creatinine Range is based on estimated GFR of 30-90 ml/min/1.73m²

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)]

Eligibility for Cohort 2 was determined by obtaining two estimated GFR measurements, with a value between 45 to 90 ml/min/1.73m². 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.

Table 4.2d, 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/1.73m²

Table 4.2.e, 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|1.73m² 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)]

Eligibility for Cohort 3 will be determined by having a Non-Glomerular diagnosis of CKD with a 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, at least two or more conditions must be met as outlined in the inclusion criteria Section 4.3. 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|1.73m² 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|1.73m² for children of different heights who are 2 years old and older.

4.3 ELIGIBILITY/INCLUSION CRITERIA

Children must meet the following criteria to be eligible to participate in the CKiD study:

- 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/1.73m² for Cohort 1 OR an estimated GFR between 45 and 90 ml/min/1.73m² 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 will be enrolled (i.e., 150 within each) and the study will place 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 abnormal imaging/biopsy must have occurred after the initial 6 months of life and must not be secondary to a current or resolving 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
 - Hyperkalemia (high levels of potassium in blood)
 - Renal glycosuria (glucose in the urine)
 - Metabolic acidosis
 - Renal tubular acidosis
 - Tubular proteinuria
- Abnormalities detected by kidney biopsy or imaging
- Abnormal kidney function
 - Age < 2 years old: serum creatinine >0.4 mg/dL in the last 6 months
 - Age ≥ 2 years old: eGFR <90 ml/min/1.73m² in the last 12 months
eGFR=41.3xheight[meters]/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

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. Children will be excluded if they meet any of the following 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., Down syndrome)
- History of Severe to Profound Mental Retardation (i.e., IQ < 40, significant impairment in adaptive functioning 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

4.4 RECRUITMENT OF ADDITIONAL AFRICAN-AMERICAN CHILDREN

After reaching the original recruitment goal of 540 children, the cohort was comprised of a 15% African-American population. So the study continued to recruit an additional 60 African-American children, which will result 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 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.

4.5 RECRUITMENT STRATEGIES

Recruitment sources and strategies will vary from site to site. Each clinical site will identify potentially eligible participants via recruitment sources and strategies available at their particular site. These may include, but are not limited to:

- Automated laboratory database searches for eligible patients (see Section 4.5.1)
- Referrals from physicians or specialty centers of potential participants (a sample of a Doctor's script is shown at the end of this section)
- Self-referral of potential participants who may respond to the study brochure/poster or other form of advertising
- Self-referral of potential participants who hear about the study from relatives or friends

Specifically, some sites may recruit participants primarily from their current clinic population, approaching parents and children at the time of their clinical care visits (assuming adequate time is available to obtain consent and complete the baseline visit.) Under this scenario, sites would have complete access to medical records, allowing them to determine eligibility on the same day as the baseline visit. Other sites may recruit participants from referrals, requiring those sites to request medical records for abstraction of GFR measurements. Children recruited in this manner require a separate pre-eligibility visit, followed by chart abstraction.

Sites should utilize eligibility procedures that best fit their site's enrollment plan. Whether on the same or separate days, eligibility and baseline visits should contain the following forms and proceed in the following order:

a. EL Form: Eligibility Form

This form is completed by site personnel to determine whether or not a child is eligible for enrollment into CKiD. To be deemed eligible, children should have a completed EL Form that indicates they are eligible and that they have agreed to enroll into CKiD.

If the site identifies an eligible child and they obtain written consent/assent, the EL form should be completed in its entirety, scanned and emailed to the CCC.

b. If the site identifies an eligible child but written consent/assent has **not yet** been obtained (i.e., family/child verbally expressed interest in participating in the study), an EL form must be partially completed with only:

- the **next consecutive KID ID number**,
- **Participant's initials** and,
- **Date of screening**. The screening date is defined as the date when the child's diagnosis and medical record were reviewed to determine eligibility or the date when the site discussed the CKiD study with the family.

No other data can be recorded on the form until written consent/assent has been obtained. This partially completed form must be scanned and emailed to the CCC. The site should keep the partially completed form. **Once written consent/assent is obtained, sites must complete the remainder of the EL form, scan it, email it to the CCC and again keep a copy of the completed form stapled.**

c. An EL form should not be completed if the site identifies an eligible child but the family/child does not agree to participate in the study (i.e., is not interested and declines to provide written consent/assent). A refusal form (REF) must be completed instead. For eligible families/children who had previously expressed interest in the study (verbally

agreed) but thereafter decline to provide written consent, a refusal (REF) must be completed. If an EL form had been partially completed and a KID ID was issued it should not be reused.

- d. If after providing written consent/assent, the family/child decides to withdraw from the study (even if before Visit 1A occurs), the Disenrollment Form (DSEN) must be completed and that KID ID should not be reused.

- e. KID ID

All children enrolled into CKiD will be assigned a 6-digit KID ID on the EL form. Assignment of the KID ID will be the responsibility of the site. 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 “01” to “49” will be reserved for sites in the mid-west CCC and 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 site beginning with “001.” For example, KID ID 1-17-012 will correspond to the 12th participant enrolled in site 17 of the mid-west CCC and represents a participant enrolled during first phase of enrollment (cohort 1).

- g. Interview Forms / Medical Exams / Laboratory specimens and tests

See Section 6 (“Overview of the Baseline Visit”).

- h. Substudy Recruitment

Substudy recruitment should follow the same procedures outlined for the entire cohort.

4.5.1 Recruitment Method: Automated laboratory database searches for eligible patients.

- Establish a Microsoft Excel database (Screening log) for entering prospective patient data
 - Column Components:

Screening Date	MRN	Name	DOB	AGE (6 m - 16 y)	Exclude if Transplanted or on Dialysis within the last 3 months (see EI form for complete list of all exclusion criteria)	CKD onset/diagnosis less than 5 years ago (Note that the onset for congenital renal conditions is the date of birth) (Y/N)	CKD Non-G diagnosis (write in diagnosis) For participants with a diagnosis listed below, conditions in the shaded fields are not necessary. All other NG diagnosis must meet 2 or more of the conditions in shaded fields. Branchio-oto-Renal Disease/Syndrome Cystinosis Medullary cystic disease/ juvenile nephronophthisis Methylmalonic Acidemia Oxalosis Polycystic kidney disease (Autosomal recessive)
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Condition must be noted after the initial 6 months of life and not secondary to a current or resolving kidney injury.					
Up/c < 2 years > 0.5 ≥ 2 years > 0.2 (Y/N)	Hematuria 2 values at least 3 months apart Dip ≥ +1 or Micro ≥ 5 (Y/N)	Renal Tubular Disorders Hyperkalemia Glycosuria, Metabolic Acidosis, Renal Tubular Acidosis, or tubular proteinuria (Y/N)	Abnormal Kidney Function Age <2 creatinine >0.4 Age ≥2 -GFR < 90 (Y/N)	Hypertension Physician diagnosed, current treatment for HTN, or hypertension or BP > 95th percentile on 2 occasions (Y/N)	Abnormal Biopsy or Imaging (Can be noted at any age) (Y/N)

Eligible? (Y/N) If participant agrees complete EL form. If they decline, complete Refusal form	Notes/Comments
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- Obtain a list of patients scheduled for clinic appointments in the following week
- Obtain a list of CRI patients, and specifically those with a non-glomerular diagnosis (if available at site. ICD-9 and ICD-10 codes are available on the Eligibility Form Q x Q for those with a method of checking the medical record for specific diagnosis codes).
Enter patient demographics and diagnosis (obtained through the Electronic Patient Record database) on the screening form
 - If Patient has a Glomerular diagnosis → Ineligible
 - If Patient is a Transplant Recipient or has had dialysis treatment within the past three months → Ineligible
 - If Patient is < 6 months old or > 16 years old → Ineligible
 - If onset of disease/diagnosis occurred > 5 years ago → Ineligible
 - Patients with certain non-glomerular diagnoses need to meet 2 additional clinical conditions establishing CKD to qualify for the study. If they criteria due to a resolving clinical condition → Ineligible
- For “Possible Candidates”
 - Review ALL inclusion/exclusion criteria listed on Eligibility Form
 - Ask patient’s physician if the patient would be a good candidate for the study
 - Physician or coordinator can explain study and obtain consent at the patient’s next visit
 - If patient does not meet 2 of the 6 additional clinical conditions, but it thought that they may become eligible with future lab results, it may be advantageous to periodically check for test results that may fall within the allowed range.
- Make contact to inform patient of his/her eligibility or ineligibility for the study.
- If patient is eligible, provide him/her with a choice of days for Baseline Visit 1A after checking availability with the GCRC or clinic.

4.5.2 Recruitment Method: CKiD Summary Sheet

The CKiD Summary Sheet is a one-page document that summarized the different components of the study. To introduce potential participants and their families to the CKiD study, clinical sites can mail the CKiD Summary Sheet. The physician can also use the summary sheet as a reference tool when approaching potential participants and their families. The CKiD Summary Sheet includes the following:

Who is Eligible?

-Children 6 months -16 years of age with chronic kidney disease

- 1) Why is this study being done?
 - a. This research is being done to identify what factors help kidneys stay healthy or cause kidney function to decline in children, and to see how kidney problems affect a child's brain development and behavior, heart function, growth and general well-being.
- 2) How many children will be involved?
 - a. We hope to enroll 1080 children at 50 medical centers across the United States and Canada.
- 3) If you decide to participate, what will you have to do?
 - a. Attend up to 4 study visits – There will be one study visit each year, except during the first year when there will be two. Most visits will last about 4 hours.
 - b. Participate in the following procedures:
 - 1. To study kidney function:** We will perform some routine blood tests such as creatinine. If you choose, we can also do an iohexol GFR Test, in which we inject an x-ray dye into the vein and draw 2 small amounts of blood a few hours later. When an iohexol GFR test is to be done, the study visit will last about 7 hours.
 - 2. To study brain function:** We will ask you to fill out some questionnaires and some other tests will be given to your child by a clinical child psychologist.
 - 3. To study heart function:** We will measure blood pressure during a physical exam at each study visit. We will also use an Ambulatory Blood Pressure Monitor, which is a light-weight blood pressure cuff that you would wear for 24 hours. Additionally, we will perform an echocardiogram, which uses ultrasound to take pictures of your heart. In some children, we will also perform a cardiac MRI which uses magnets to take pictures of the heart. We will also do blood tests (such as cholesterol) that look at risk of heart disease.
 - 4. To study growth:** We will measure height and weight during a physical exam at every study visit. You or your child will answer questions about appetite and diet and we will also do blood tests (such as calcium) that relate to growth at every study visit. Additionally, we will perform a fitness test that measures hand grip strength as well as evaluate physical activity levels.

You will be compensated for your participation. If you are interested in joining this study please contact the study coordinator below for more information.

<< Insert Name >>

CKiD Study Coordinator

Tel:

Email:

4.5.3 Recruitment Method: Doctor's Script based on CKiD Summary Sheet

Physicians can use the CKiD summary sheet as a reference tool when approaching potential participants and their families. Below is a drafted script that incorporates the key points outlined in the CKiD Summary Sheet.

Doctor Script for the CKiD Study: We would like to invite your child to participate in a research study that is being carried out by the Pediatric Nephrology clinic. The study is called CKiD, which stands for Chronic Kidney Disease in Children. We are asking children 6 months to 16 years old who have had Chronic Kidney Disease (CKD) for less than 5 years to join this study. We have enrolled approximately 900 children at 50 different places around the US and Canada to be in the study, and we hope to enroll about 190 more. About (number of children enrolled) children will be asked to participate at this institution.

This research is being done to investigate what factors cause CKD to become worse in children, and to see how CKD affects a child's brain development and behavior, heart function, growth and general well-being.

This is not a treatment study and it will not directly benefit your child. However, this study will give us more information about the function of your child's kidneys, heart, and brain, and will help children like him/her in the future.

If you decide to allow your child to participate your child will be asked to:

A) Attend up to 3 study visits.

There will be one study visit per year except during the first year when there will be two study visits. Study visits are each about 4 hours on length. If you choose to have an iohexol test done to measure your child's kidney function, every other visit will take about 7 hours.

B) Participate in the following procedures:

1. To study kidney function: You may choose for your child to have a GFR test which directly measures how well a kidney is working. For this test we inject an x-ray dye into one arm and draw 2 small amounts of blood from the other arm over a few hours. We will also perform some routine blood tests for all participants at each visit.

2. To study brain function: We will ask you to fill out some questionnaires and take some tests that will be given to you by a clinical child psychologist.

3. To study heart function: We will measure blood pressure during a physical exam at each study visit. We will also use an Ambulatory Blood Pressure Monitor, which is a light-weight blood pressure cuff that you would wear for 24 hours. Additionally, we will perform an echocardiograph, which uses ultrasound to take pictures of your heart. At each study visit, we will also do blood tests (such as cholesterol) that look at risk of heart disease.

4. To study growth: We will measure height and weight during a physical exam at every study visit. You or your parent will keep a three-day diet record each year, and we will also do blood tests (such as calcium) that relate to growth at every study visit.

5. (Optional) Donate biological and genetic samples: We will ask if you would like for your child to donate a small amount of blood that will be saved for future research of CKD.

For your participation in this study, we will give you (honorarium amount) for completion of each Study Visit 1A, or V2 and (honorarium amount) for completion of Study Visit 1B. If you chose to do the GFR test, we will give you an additional (honorarium amount) for completion of each Study Visit 1A, V2.

Do you think you and your child would be interested in joining this study?

4.6 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. In order to retain participants, pleasant, attentive and responsive staff should make efforts to provide 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 birthday cards, holiday cards, newsletters, and small gifts; recognition certificates for 5 year and 10 year participation milestones; creation of a form to document volunteer hours for time spent at study visits; the provision of selected study test results which may be used to supplement the clinical care of a participant; and a modest honorarium for participation. Consistency among staff members and collecting back-up contact information (e.g., grandparents' address) on participants may also improve retention rates.

It is anticipated that over the course of the study CKiD participants may withdraw from the study. This 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 encouragement 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.

The continued follow-up protocol, also known as the Continued Follow Up Protocol (PIP) or on-line survey (ePIP), should be offered to all participants who have successfully completed a study visit but are not expected to be able to return for a future study visit. This protocol was developed to allow the study to continue to obtain information on the health status and long-term outcomes of chronic kidney disease among participants who exit the regular visit follow-up portion of the study pre-maturely. Participants will be given the option to participate in the post renal replacement therapy protocol or continued follow-up protocol after they have renal replacement therapy, which by protocol defines them as ineligible to complete further regular study visits. The continued follow-up protocol should also be offered to participants who are pregnant, unable to reach, no longer desire to attend regular study visits (i.e., withdrawal) or who are no longer able to complete regular study visits. For additional information on the continued follow-up protocol refer to MOP Section 8: Additional Visits.

Additionally, in CKiD III linking information to public health databases (such as Census and United States Renal Data System (USRDS)) was implemented to further support obtaining information about long-term health outcomes of CKD among participants who have initiated renal replacement therapy or who have transitioned to adult care and are no longer able to attend visits at the pediatric institution.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY
SECTION 5: GETTING STARTED PRIOR TO BASELINE VISIT

5.1 OBTAINING IRB APPROVAL

Each clinical site will need to complete their Institutional Review Board’s (IRB) or Research Ethics Board (REB) application and be approved by their IRB/REB before the clinical site can enroll participants into the CKiD study. It is mandatory that a copy of the institutional IRB/REB approval for the CKiD study and a copy of the approved consent form and assent form (See Section 6.2) be sent to the clinical coordinator center (CCC) prior to proceeding with the baseline procedures. To aid in this process a prototype IRB application with sample questions and responses particular to the CKiD study was developed (See Sections 5.10 and 5.11). It is recognized that clinical site IRB’s have varying requirements and questions and therefore responses may differ between clinical centers. The prototype IRB application is intended as a guideline that most clinical centers could follow.

5.2 OBTAINING CRC/CRU APPROVAL

To cover some of the costs for conducting the CKiD study it is recommended that clinical sites that have a Clinical Research Center (CRC) or Clinical Research Unit (CRU) apply for their services and support. A prototype CRC/CRU application has been developed to aid in the application process (See Section 5.9). The prototype application is intended as a guideline that most clinical centers that have a CRC/CRU could follow.

5.3 COORDINATION OF VARIOUS DEPARTMENTS

Some of the procedures and tests that will be done in the CKiD study may require the coordination of several departments within the clinical site. To ensure that study visits are completed, the following departments may need to be contacted prior to enrollment:

<u>Procedure/Test</u>	<u>Department to Contact</u>
Echocardiography	Cardiology Dept. and/or Echo Lab
Carotid Intima-Media Thickness	Radiology Dept., Cardiology Dept. or Echo Lab
Vascular Testing	Personnel responsible for Vascular testing (Dept. varies)
Cardiac Magnetic Resonance Imaging	MRI or Radiology Dept.
Core Neurological Tests	Developmental and Behavioral Sciences Neurology and/or Psychology- Clinical Child Psychologist Pediatric Neuropsychologist
Storage & Preparation of Iohexol	Research Pharmacy/Investigational Drug Services

Once the site has identified the individual(s) who will perform the procedure(s), the study coordinator must add their information to the CKiD directory. To add, update or delete personnel information to CKiD directory, study coordinators must do as follows:

- Go to the CKiD website: <https://statepi.jhsph.edu/ckid/>
- Type in username and password (If you do not have or can not locate your username and password, contact Judith Jerry-Fluker at jjerry@jhu.edu.)
- Click on Directory.
- Click on Updates, deletions, and additions.
- Fill out the On-line Personnel Information Form.

5.4 REQUIRED DOCUMENTS PRIOR TO ENROLLMENT

The following lists the required documents that need to be sent to the CCC prior to enrollment:

- Human Subjects Certification for the clinical center Principal Investigator (PI) and study coordinator
- Copy of the institutional IRB or REB approval
- Copy of the institutional IRB or REB approved consent form and assent form
- CRC or CRU approval (if applicable)
- Signed Subcontract
- Clinical Site Contact Form

5.5 STARTER PACKAGE AND CBL START-UP KIT

5.5.1 Starter Package

After the clinical site sends a copy of their IRB approval to their respective coordinating center, the CCC will mail the site a CKiD starter package with a congratulations letter. The starter package will include the following items electronically or via hard copy:

- These documents are provided electronically. However, in the event that hard copies are requested or given, the CCC distributes the information in a Clinic Binder (The binder assists sites in organizing CKiD documents):
 - Front Pocket of binder:
 - Contact Information
 - Dividers for :
 - IRB/REB Approval
 - IRB/REB Approved CKiD Protocol
 - Amendment
 - IRB/REB Approved Consent/Assent
 - IRB/REB Application
 - IRB/REB Correspondence
 - CRC/CRU Application
 - CRC/CRU Approval & Correspondence
 - General Correspondence
 - Screening Log to help track potential participants
 - Eligibility Form
 - Refusal Form
 - Enrollment Log
 - Shipping Log

- Back pocket of binder
 - Inclusion/exclusion information, contact information, and study timetable
 - Tanner Stage information
 - Table 5.4.1.a & Table 5.4.1b found in protocol
 - Instructions for shipping completed Forms Binders to the CCC
- 5 White Visit Family Binders (Provided on request. Binders may be given to participants to keep all CKiD information together such as signed consent forms and visit instructions)
- Supplies:
 - (2) Sharpie waterproof markers to document date of specimen collection on laboratory tubes
 - Mabis Medic Kit5-Aneroid blood pressure device with cuffs
 - 5 disposable tape measures
 - (1) SECA 218 (previously 402) baby band to measure head and arm circumference for children less than 3 years old
 - Tanner Stage Orchidometer (green beads)
 - Grooming kit with stainless steel nail clippers and scissors for smaller children and a large stainless steel nail clipper for the larger children
 - Clipboard (to aid parents in completing study forms)
 - Dynamometer (device used to measure hand-grip strength)

*If the study coordinator is missing any of the items mentioned above, they should contact their respective Clinical Coordinating Center Project Director (Jacqueline Ndirangu or Julie Starr).

When the clinical site study coordinator has enrolled a participant, they should email their CCC Project Director and fax or scan and e-mail the potential participants Eligibility Form.

The CCC Project Director will confirm that the participant is eligible for the study, and confirm the KID ID assigned is correct.

5.5.2 CBL Starter Kit

Each clinical site with IRB approval will review a Central Biochemistry Laboratory (CBL) Starter Kit. The CBL will also send the clinical site's pharmacy an "emergency" iohexol, if applicable. The emergency iohexol can be used in rare cases when the CBL is unable to mail the iohexol to the site prior to the study visit. For further information on storing and using iohexol, see Section 11. The CBL starter kit will include:

- Timer for pulse measurement, and Iohexol GFR test
- 2-SSTs for the 2-point iohexol samples (if applicable)
- 1-extra SST for repeat draw in the incidence of a difficult draw at any of the 2 points
- 2 cryovials for iohexol serum samples (if applicable)
- 2-tiger top SST for blood collection of time = zero blood, prior to infusion of iohexol
- 1-orange top transport tube for renal panel
- 1-plastic blue screw-top cryovial for Cystatin C
- 1-large blue top tube for CBL urine specimen
- Disposable pipette
- Sanizide cleaner for disinfecting nail clippers and scissors
- Gulick retractable tape measure
- Blister pack and absorbent sleeve for mailing specimens
- 1 specimen transport zip loc bag with absorbent gel pad
- Pre-printed Federal Express labels
- IATA shipper for diagnostic specimens (with instructions)
- Assembly instructions for mailing kit to CBL

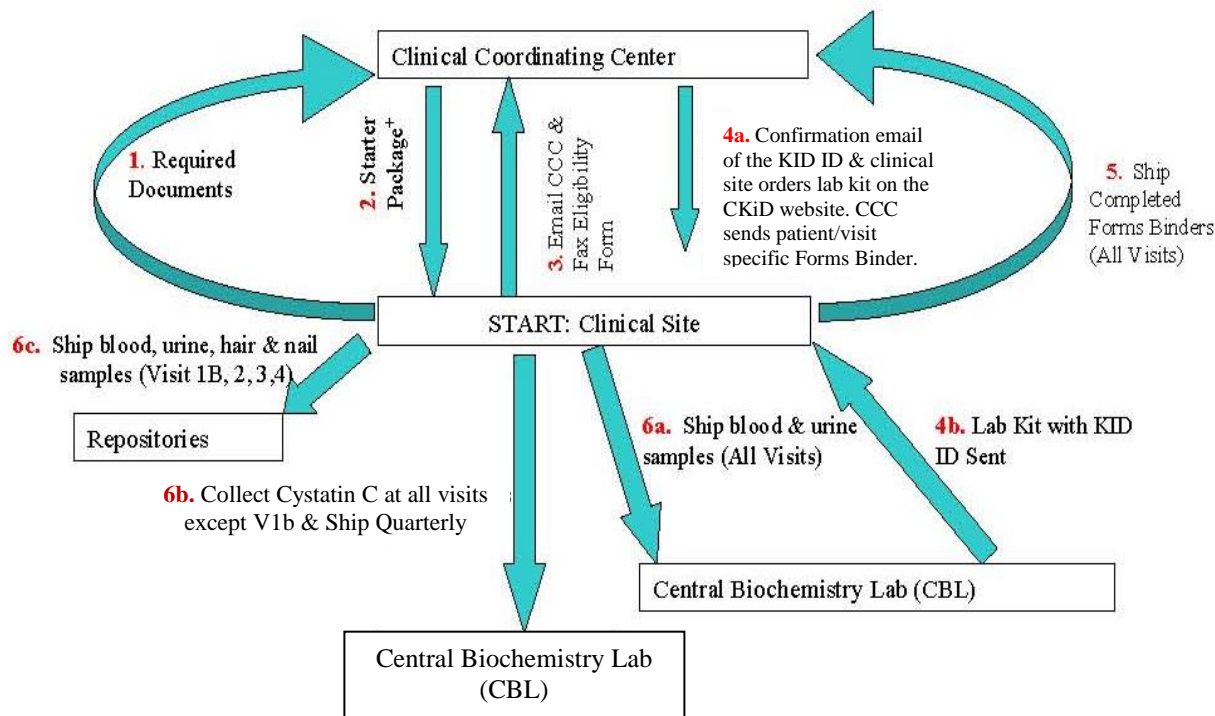
5.6 REQUESTING SUPPLIES FOR A STUDY VISIT

When a participant is scheduled for a study visit, the study coordinator must log-onto the CKiD website: <https://statepi.jhsph.edu/ckid/> and order the visit-specific labkit from the Coordinator's Corner. Additional visit supplies (e.g. Iohexol, 1st morning urine supplies, ABPMs and dry ice shippers) may also be requested here when needed. Once the request is submitted on the website, an email notification will be sent to the appropriate study staff who will then ship the required items to the study coordinator. The CCC will also be automatically notified of the coordinator's request and ship a Visit-Specific Forms binder to the clinical site.

5.7 FLOW OF COMMUNICATION

Below is the CKiD flow of communication. It outlines the communication between the clinical sites, clinical coordinating centers, data coordinating center, CBL and Repositories.

Diagram 5.7.1: Flow of Communication



*Required Documents: A) IRB Approval; B) Approved Consent; C) Approved Assent (if applicable); D) GCRC Approval (if applicable); E) Human Subjects Certification for PI and Coordinator; F) Completed Clinical Site Contact Form; G) Signed Subcontract

+Starter Package includes: Clinic Binder, 5 Visit 1A Family Binders, CKiD Clipboard, CKiD Duffel Bag with CKiD Supplies (ie Mabis Medic Kit5-Aneroid Blood Pressure Device, tanner beads, etc.)

Step 1: Clinical site submits required documents to the CCC.

Step 2: Starter package is sent to clinical site.

Step 3: Clinical site emails CCC when CKiD participant is enrolled and faxes or scans and e-mails Eligibility form.

Step 4: CCC replies to clinical site to confirm eligibility and correct KID ID assigned. Clinical site orders lab kit on the CKiD website. Information should include the day of scheduled visit, coordinators contact information, and site pharmacist contact information. This order serves as the request for the CBL to send the lab kit and also notifies the CCC to send the Forms Binder.

Step 5: When the visit occurs, the clinical site completes forms in the Forms Binder and returns the completed forms to CCC for data entry.

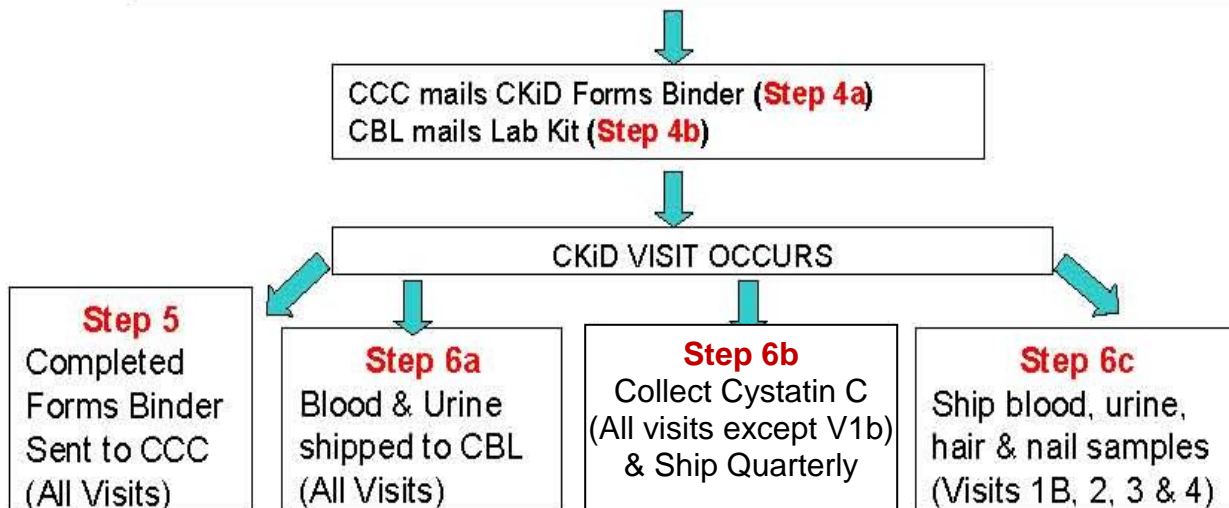
Step 6: Depending on study visit, site ships specimen to different laboratories. See Section 11 for details on Sample Handling and Collection.

Step 3

Clinical Site emails CCC when CKiD participant is enrolled and faxes or scans/emails Eligibility Form

Step 4

- CCC replies to clinical site and confirms correct KID ID assigned.
- Clinical site orders lab kit on the CKiD website.
Information should include:
 - Visit number
 - Date of visit
 - Clinical site coordinator's name, address phone number
 - Clinical site pharmacist's name address, phone number
- This order serves as the request for the CBL to send the lab kit and also notifies the CCC to send the Forms Binder.



5.8 CKiD PROTOCOL AMENDMENT

Amendment 1: CKiD Protocol Amendment Table-lists the changes from 10/07/04 version of the protocol to 04/01/05

PAGE #(S) ON UPDATED PROTOCOL	CHANGE(S)	RATIONALE (IF APPLICABLE)
9-11	Changed 54 sites to 57 sites; Principal Investigator names and sites added to table	Suggestion to update the clinical sites and PI's that are involved in the CKiD study
9	Additional funding is provided by the National Institute of Neurological Disorders and Stroke, the National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute	Suggestion to further clarify national funding resources
12	<ol style="list-style-type: none"> 1. Lab results to be faxed from central laboratory to the clinical site 2. Highly sensitive C reactive protein has been updated to wide range C reactive protein throughout the protocol 3. Participants will be given the option to contribute samples beginning at study visit 1b. 4. Blood and urine specimens will be collected at baseline and at each annual follow-up visit. 5. Nail clippings and hair samples will be collected at baseline. 6. Also deleted: "Each repository has obtained a Certificate of Confidentiality from the Federal Government to assure privacy." 	<ol style="list-style-type: none"> 1. Suggestion to clarify the reporting of lab results. 2. Suggestion to update the terminology for C reactive protein. 3, 4, 5. Suggestion to modify and clarify the optional biological and genetic specimens to be collected for storage at the repositories and the schedule of collecting these specimens. 6. We plan to obtain a Certificate of Confidentiality for the entire study. See rationale page 86-87.
14-15	A Laboratory/Specimen Working Group has been established (Section 3.6.4.3 of the protocol)	Suggestion to add a Laboratory/Specimen Working Group as a study-wide subcommittee.
16	"Submission of a concept sheet requires that (a) key personnel are certified in the NIH OHSR or equivalent training course, and (b) one CKiD participant is enrolled in the main study."	To expedite the process of concept sheet submission.
17	Deletion of, "If a writing committee member does not actively participate in the writing and/or review process,..." and Addition of, "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.."	Suggestion to revise the criteria for removing members of the writing committee
19	Table 4.2 eGFR divisions and corresponding text changed: from 40-60 to 40-59, and from 30-40 to 30-39	To clarify the divisions of the estimated GFR

20	<ol style="list-style-type: none"> 1. 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; 2. Children aged 1-16 years, inclusive, are eligible; 3. Eligibility details modified to state that eligibility will be determined by obtaining two estimated GFR measurements, with a value between 30 to 75 ml/min/1.73m². The first measurement must be within the past six months and the second measurement within the past twelve months; 4. Clarified adolescent males as those greater than or equal to 13 years old (p.20 and 37) 	<ol style="list-style-type: none"> 1. Suggestion to include these groups to make our study population more representative of the general population, as long as the majority of study data can be collected 2. The Steering Committee believes that allowing 16-year-olds to participate will not compromise study data, and will help the study reach the recruitment goal 3. To provide a wider time range for GFR measurements without compromising the study data. 4. To clarify what age is considered “pre-pubertal” and “adolescent” in order to ensure accurate calculation of estimated GFR
21	Details added to exclusion criteria regarding history of cancer, HIV, pregnancy, allergy to Iohexol, and mental retardation.	Suggestion to further refine and clarify the eligibility criteria of study participants.
22	Two estimated GFR measurements, with a value between 30 to 75 ml/min/1.73m ² , will be required for study enrollment. The first measurement must be within the past six months and the second measurement within the past twelve months.	To provide a more specific time range for GFR measurements.
24	The protocol has been changed to state, “Each year, the participating child will be given a small gift, such as a gift certificate, ...”	We will provide a book store gift certificate instead of a book to allow children more choice in their book selection.
28	<p>Changes made to Table 5.4.2a:</p> <ol style="list-style-type: none"> 1. Added footnote d 2. Added a footnote to explain the “neuropsychological assessments for high-risk children” listing in the table 3. Family Binder to be sent out before each visit 4. Diet history added to table 5. Pregnancy tests clarified as local pregnancy tests 	<ol style="list-style-type: none"> 1. Added footnote d to clarify option of obtaining local BMP and urine tests in addition to central tests; 2. “Neuropsychological assessments for high-risk children” explained in footnote to condense table; 3. Suggestion that Family Binders before each visit will help participants remember their appointment, explain the visit, and tell them what information to bring from home 4. Diet history was not listed in the previous version of the table 5. Clarification was needed about where pregnancy tests will be run

29	<ol style="list-style-type: none"> 1. Reformatted timetable for collection of repository samples; 2. Added footnote c regarding genetic specimen 	<ol style="list-style-type: none"> 1. To clarify that “Biological Specimens” include hair, nails, blood and urine and to change the collection of the Biological Specimens to V1b 2. Suggestion to make reasonable effort to collect Genetic Blood Specimen at another visit if not collected at V1b
32	Removed from Section 6.1: “Additionally, there will be semi-annual follow-up telephone contacts”	Suggestion to delete semi-annual follow-up telephone contacts to simplify the procedures for the coordinator and to maintain the focus of the study on patients with chronic kidney disease.
33	<ol style="list-style-type: none"> 1. Amended Section 6.1.3 regarding assessment of Physical Activity; 2. We will now be using physical activity questions from the 2005 Youth Risk Behavior Survey (YRBS). 	Suggestion that previous-day recall may not be as accurate as answers obtained with the more general YRBS
34	Nail clippings and hair samples to be collected at visit 1b	Changed from V1a; eases the burden on the study coordinator at V1a
35	Core tests to include urine creatinine	Suggestion to include this important test as a standardized core procedure
37	For clinical sites requiring immediate results, serum creatinine will be obtained locally as part of the basic metabolic panel.	Suggestion to clarify the inclusion of serum creatinine in local basic metabolic panels.
38-39	<ol style="list-style-type: none"> 1. Details added to first morning urine collection 2. For clinical sites requiring immediate results, the protein to creatinine ratio will be obtained locally 	<ol style="list-style-type: none"> 1. To provide details regarding collection of urine if container is not provided by clinical site, and if urine is not collected at home 2. To clarify that the protein to creatinine ratio may be obtained locally if the site requires immediate results
39	<ol style="list-style-type: none"> 1. Basic metabolic panel and serum glucose labs are obtained locally only if immediate results are needed 2. A BMP will be run centrally at baseline and at all annual visits. Serum glucose will be measured centrally at baseline and at all annual visits 3. Added to Section 6.2.1.7: “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.” 4. Added section 6.2.1.1 to detail Urine Pregnancy Test 	<ol style="list-style-type: none"> 1. Suggestion to include provision of an optional BMP should the local PI want immediate results 2. Suggestion to clarify the visits at which the basic metabolic panel and serum glucose will be obtained 3. Suggestion that CBC results from past 30 days will be adequate for the study and will lessen the burden on patient and local site 4. Suggestion to include details to clarify frequency of pregnancy testing and handling of positive pregnancy tests
41	<ol style="list-style-type: none"> 1. The Abbreviated, not Screener, version of the Wechsler Individual Achievement Test-Second Edition will be used; 	<ol style="list-style-type: none"> 1. The WIAT-II-A comprises three key subtests that best represent the core domains of reading, writing, and arithmetic.

	<ol style="list-style-type: none"> 2. Alpern-Boll Developmental Profile II (DP-II) has been removed from the battery of tests; 3. CDI and BRIEF added to core tests for behavioral assessment (p. 41 and 45) 4. The Behavior Assessment System for Children- Second Edition (BASC-2) will be used in place of the BASC (p. 41 and 44) 	<ol style="list-style-type: none"> 2. The DP-II is currently being revised and the neurocognitive subcommittee felt that it would be best not to use an instrument that will be considered outdated by the time CKiD is over; 3. Suggestion from the neurocognitive subcommittee to include measures to assess depression and executive functions within the context of home and preschool environments 4. Suggestion to clarify the BASC test to be used as BASC-2.
41, 45	The Child Behavior Checklist (CBCL) has been removed from the battery	Steering Committee feels that other surveys will be more comprehensive than the CBCL
42	Minor rewording to Section 6.3.1.1.1;	To clarify that the Mullen Scales of Early Learning is a measure of development and cognitive function and that children over the age of 29 months will not receive the Mullen Scales of Early Learning
43	Description of Alpern-Boll Developmental Profile II removed	The DP-II is currently being revised and the neurocognitive subcommittee felt that it would be best not to use an instrument that will be considered outdated by the time CKiD is over.
44	Diagram 6.3.1.2 amended by removing CBC-L and adding the CDI, BRIEF-P, and BRIEF	To make the diagram reflect the changes in the neurocognitive battery of tests
45-46	<ol style="list-style-type: none"> 1. Added descriptions of Children’s Depression Inventory (CDI), Behavior Rating Inventory for Executive Functions – Preschool Version (BRIEF-P), and Behavior Rating Inventory for Executive Functions (BRIEF) 2. The Clinical Evaluation of Language Fundamental- 4th Edition (CELF-4) will be administered 	<ol style="list-style-type: none"> 1. To provide PI’s, study coordinators, psychologists, and IRB officials with in-depth details of each of the new additions to the neurocognitive battery 2. To clarify the specific CELF test that will be administered
55	Details added about fasting but not thirsting before lipid studies	To clarify instructions for fasting but not thirsting
58	<ol style="list-style-type: none"> 1. Three-day diet records will be obtained on a yearly basis beginning at the second baseline visit (V1b); 2. 3-day diet history must include two weekdays and one weekend day; 3. Written food records will be sent from the parents to the clinical site study coordinator, not directly to the DCC; 4. Added the sentence, “Only select clinical sites will perform bone biopsies.” 	<ol style="list-style-type: none"> 1. Suggestion to modify the timing of the 3-day diet record to visit 1b to give the coordinator or dietician a chance to explain the procedure at visit 1a. 2. Diet of 2 weekdays and 1 weekend day will be most representative of overall diet 3. This procedure will reduce the burden on parents 4. To highlight the fact that bone biopsies will not be done at each clinical site

78	New study coordinators will be able to review a training video, but not necessarily the video of the training meetings that took place in Nov 2004	Plans are being made to assemble a DVD highlighting the major components of the CKiD protocol and study visits
83	Added, “It is recommended that a follow-up letter documenting information discussed by phone should also be sent to the participant’s primary nephrologists.”	Suggestion to modify the wording of the follow-up process for immediate alerts. The CKiD study will not track this follow-up at the clinical sites. This is a recommended follow-up.
84	Deletion of the sentence, “It is also recommended that BP and Pulse be monitored hourly after the Iohexol injection for the course of the study visit.”	BP and Pulse will be monitored in accordance with recommendations of the Steering Committee.
86	1. The repositories have been added to the group of centers that have the responsibility to maintain confidentiality 2. The DCC, clinical coordinating centers and repositories do not have access to the log kept at the clinical sites that has participant names, participant ID numbers, and pertinent registration information	1. Suggestion to include the repositories in the group of centers that are responsible for maintaining confidentiality. This will clarify that they maintain confidentiality like the clinical sites, the clinical coordinating centers, and the DCC. 2. Suggestion to clarify that the logs will only be accessible to the clinical sites.
86-87	A Certificate of Confidentiality will be obtained for the entire study from the National Institutes of Health.	Suggestion to add information regarding the Certificate of Confidentiality
88	Laboratory/Specimen Working Group added	To identify the members of this subcommittee
92	Appendix E removed from protocol	Suggestion to remove Appendix E from the protocol. These alerts will be captured on the clinical research forms and will be reported to the appropriate personnel as indicated on pages 83-84.
Throughout the protocol		Suggestion to make minor grammatical changes throughout the protocol

January 2006 Amendment (Amendment 2): CKiD Protocol Amendment Table-lists the changes from 04/01/05 version of the protocol to 01/01/06

PAGE #(S) ON UPDATED PROTOCOL	CHANGE(S)	RATIONALE (IF APPLICABLE)
iii	Added “6.2.1.12 Optional Tests Performed Locally”	To clarify optional versus study tests. A separate section has been added regarding optional tests performed locally (Section 6.2.1.12)
All	Deleted “Iohexol” and replaced with “iohexol” throughout the protocol for consistency. Deleted “injection of iohexol” throughout the protocol. Added “infusion of iohexol” throughout the protocol.	Instructed by the Central Biochemistry Laboratory.
5	Protocol changed to “This study will obtain baseline measurements of cognitive function within 6 months of the baseline GFR assessment, depending on the age of the child.	To provide more flexibility in scheduling patient study visits.
10-11	Tables 3.2.1 and 3.2.2 updated.	To update the names of the participating clinical sites and associated Principal Investigators.
11	Terminology changed from “basic renal panel” to “central renal panel”.	To clarify the labs needed and maintain consistency in terminology.
12	Protocol changed to “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.” Deleted “The collected samples will be sent to the central repository for biologic specimens, from baseline visit to central repository for genetic material, and from the DCC to the central repository for data.” Protocol changed to “Fisher BioServices” Deleted “McKesson” and “s”	To clarify the type of samples/data to be collected and sent to specific repositories.
16	Deleted “that”, “are”, “b”, “an, and “may be requested by the SC to review the proposal prior to the SC review”.	

	<p>Added “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).</p>	<p>To clarify the process once a concept sheet is submitted to the DCC.</p>
19	<p>Protocol changed to “270”</p> <p>Deleted “300”</p>	<p>To provide the updated number of patients.</p>
20	<p>Protocol changed to “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.”</p> <p>Deleted “in girls and in pre-pubertal boys” and “in adolescent males (13 years and older)”</p>	<p>To provide more specific information for eGFR for infants 12 to 18 months of age.</p>
22	<p>Protocol changed to “past 18 months”</p> <p>Deleted “past 12 months”</p>	<p>To provide a broader window for eGFR measurement for eligibility to capture those patients who may only come for clinic visits at a specific site on an infrequent basis.</p>
23	<p>Table 5.2.1a name changed to “MALES and FEMALES (12 Months to 18 months”</p> <p>Deleted “MALES before 13th birthday & ALL FEMALES”</p>	<p>As above (page 20)</p>
24	<p>Table 5.2.1b name changed to “MALES (19 months to before 13th birthday) & FEMALES (19 months and older)”</p>	<p>As above (page 20)</p>
25	<p>Table 5.2.1c name changed to “MALES after 13th birthday”</p>	<p>As above (page 20)</p>

26	<p>Protocol changed to “Participants will be scheduled to return within 6 months of the baseline GFR assessment, depending on the age of the child.....”</p> <p>Added “Each study visit may be scheduled within a plus or minus one month window of time.”</p> <p>Deleted “6 and 12”</p>	To provide more flexibility in scheduling patient study visits.
27	<p>Protocol changed to “within 6 months”</p> <p>Deleted “between 3 and”</p>	As above (page 26).
29	<p>Protocol changed to “assessments will occur within six months after the V1a visit (i.e., the second component of visit 1 (V1b) which will take place close to midway between the first two years of the follow-up).”</p> <p>Deleted “between three to”</p>	As above (page 26).
30	Added whole blood lead and urine cadmium to table 5.4.2a.	
31	<p>Protocol changed to “The biological specimens will be stored at Fisher BioServices Corporation, the NIDDK Biosample Repository in Rockville, MD.”</p> <p>Deleted “McKesson” and “s”.</p>	To provide the recently changed name of the biological repository.
34-35	<p>Added “6.1.2 General History Information</p> <p>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 and household income data will be collected. These data will be collected by parent/guardian questionnaire using standard instruments at the baseline visit.</p> <p>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</p>	To clarify the information collected in study forms.

	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.”	
35	Deleted 6.1.2.3 “Birth and Family History: Birth weight in 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”	As above (page 34-35).
35	Protocol changed to state “Three-day diet histories will be collected at baseline and annual follow-up visits.”	To clarify and generalize that three-day diet histories will be collected at baseline. Jeff Fadrowski’s approved concept sheet.
35	Deleted “6.1.3 Physical Activity In children 12 years old and older, physical activity will be determined by the use of physical activity questions from the 2005 Youth Risk Behavior Survey (YRBS). The YRBS is a self report instrument designed to monitor categories of priority health risk behaviors among youth. [CDC 2005, Grunbaum]. Deleted “Questionnaires will be administered for smoking, alcohol and drug use in adolescents.”	As above (page 34-35).
36	Added “Pending ancillary funding and feasibility, exposure to heavy metals (e.g., lead, 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	As above (page 34-35).

	<p>samples will only be collected at the second baseline visit (V1b).</p> <p>Added “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 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 [CDC 2005, Grunbaum 2004].</p> <p>6.1.7 Physical Activity For participants 12 years old and older, physical activity will also be determined by the use of physical activity questions from the 2005 Youth Risk Behavior Survey (YRBS).</p>	
37	Deleted “Electrolytes”	To clarify the fact that electrolytes are part of the Basic Metabolic Panel.
39	<p>Deleted “Injection from sub-title” Protocol changed sub-title to “Single Infusion of iohexol clearance to measure GFR” Deleted “Then, 5ml of iohexol solution (Omnipaque 300, corresponding to 647 mg iohexol per ml) will be injected over 2 min followed by 10ml of saline solution.” Protocol changed to “The complete 5.0 mL dosage of iohexol (Omnipaque 300, corresponding to 647 mg iohexol per mL) will be administered intravenously x1 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.”</p>	To clarify the dosage of iohexol and the information collected pre and post iohexol infusion.

39	<p>Added “A four sample plasma disappearance will be performed at 10, 30, 120 and 300 minutes. The four time points were determined based upon the results of the pilot study”.</p> <p>Deleted “If blood samples cannot be obtained by these methods, sampling can be performed by finger stick with collection of 250 microliters of blood into an EDTA-containing Microtainer collection tube (Becton Dickinson)</p>	<p>Dr. Schwartz recommended this addition.</p> <p>Dr. Schwartz recommended this deletion.</p>
39	<p>Added “In the event that blood samples cannot be obtained during the regular study visit (i.e., IV infiltration or inability to successfully draw 4 blood samples for iohexol), the participant will be rescheduled for a make-up GFR within a month. 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, HPLC creatinine, 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, only a 1 mL B0 blank (blood collected pre-iohexol infusion) and 4 blood samples for determining the iohexol concentrations will be collected.</p>	<p>To clarify the process of a make-up GFR visit.</p>
39	<p>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 1 mL B0 blank (blood collected pre-iohexol infusion) and 4 blood samples for determining the iohexol concentrations will be collected and sent to the CBL for processing and analysis.”</p>	<p>To clarify the process of a make-up GFR visit.</p>

40	<p>Section 6.2.1.2 Serum Creatinine: The method of obtaining confirmation of estimated GFR measurements has been added.</p> <p>Protocol changed to “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”</p> <p>Deleted “For clinical sites requiring immediate results, serum creatinine will be obtained locally as part of the basic metabolic panel.”</p> <p>Deleted “Injection from sub-title”</p>	<p>To clarify the response to an estimated GFR less than or equal to 15 ml/min 1.73m²</p> <p>As above (page 20).</p> <p>As above (page iii).</p>
41	<p>Deleted “For Clinical sites requiring immediate results, the protein to creatinine ratio will be obtained locally.”</p> <p>Deleted “Electrolytes”</p> <p>Deleted “For clinical sites requiring immediate results a basic metabolic panel will be obtained locally”</p> <p>Deleted “For clinical sites requiring immediate results, glucose will be obtained locally as part of the basic metabolic panel.”</p> <p>Section 6.2.1.5 Proteinuria and Urine Creatinine: Added “any clean container.”</p>	<p>As above (page iii).</p> <p>To clarify that the first morning urine sample should be in a clean container rather than any container.</p>

42	<p>Added “6.2.1.12 Optional Tests Performed Locally</p> <ul style="list-style-type: none"> For all tests performed centrally, the Central Biochemistry Laboratory will fax results to the clinical sites. However, if lab results are needed immediately for clinical care, those labs should be performed locally (in addition to the centrally performed tests).” 	As above (page iii).
43	Protocol changed to state that the cognitive tests are only standardized in English.	To include additional information regarding the cognitive tests.
49	<p>Deleted “...high-risk children and adolescents (GFR=30-40 ml/min 1.73m²)...”</p> <p>Deleted “...given that we suspect kidney dysfunction to have its most significant impact on the developing brain, we propose to scan children ≤ 5 years of age as well with GFR < 60 ml/min 1.73m².”</p> <p>Added “...participants between the ages of 9-16 years with an estimated GFR of < 40 ml/min 1.73m² as calculated by the Schwartz formula. In addition, these participants must display normal cognitive functioning (no mental retardation or history of special education) at study entry.”</p>	<p>Reflect changes to the Neuro imaging protocol.</p> <p>Reflect changes to the Neuro imaging protocol.</p>
53	Deleted “Dissemination”	Grammatical change.
58	Deleted “Children will be measured in bare feet. Height will be measured using stadiometer in”	To delete repetitive information.
59	<p>Protocol changed to “Three-day diet records will be obtained on a yearly basis beginning at the second baseline visit (V1b). Children and parents will be instructed on how to complete a consecutive 3-day prospective food diary. Written instructions, oral instructions, and data collection forms will be standardized [Mahan 2000]. The consecutive 3-day period must include two weekdays and one weekend day.”</p> <p>No verbage deleted, added “consecutive”.</p>	To provide clarification regarding the three-day diet records.
60	Section 6.5.2.1 Bone Biopsy	To modify and clarify the protocol for bone biopsies, which are non-core tests.

	<p>Protocol changed to state, “Each patient will undergo one bone biopsy within six months of study entry.”</p> <p>Added “Additional data generated from patients undergoing bone biopsies at the University of California- Los Angeles within six months prior to study entry will also be incorporated into the CKiD database.”</p>	<p>To include information regarding additional data to be included in the CKiD database.</p>
79	<p>Protocol changed to “All new coordinators who replace existing coordinators will be able to review a CKiD training DVD.”</p> <p>Deleted “video”</p>	<p>To update the media form used for coordinator training.</p>
84	<p>Protocol changed to state that feedback from cognitive and developmental assessments in “a timely fashion.” “A procedure for reporting such information is described in the Manual of Procedures.”</p>	<p>To clarify that the feedback will be given in a timely fashion rather than after the assessment has been completed.</p> <p>To include the fact that the Manual of Procedures explains the process of feedback.</p>
85	<p>Protocol changed to “Certain laboratory tests, such as potassium and glucose, will be performed centrally and results will not be known immediately. For this reason, certain significantly abnormal results are classified as urgent. It is recommended that for urgent alerts the primary Nephrologist is notified within 24 hours after receiving the faxed results from the Central Biochemistry Laboratory.”</p> <p>Deleted “Urgent alerts require notification of the participation and it is recommended that the participant’s primary Nephrologist within 24 hours of receipt of the results”</p>	<p>To clarify the process for responding to urgent laboratory results.</p>
86	<p>Added “Participants who turn 18 years old before the end of the study and have samples stored in the repositories, they will be re-consented per local IRB guidelines.”</p>	<p>To clarify the process for storing samples in repositories.</p>

88	Added, "All SAEs related to a study procedure will be reviewed monthly by the Steering Committee and annually by the External Advisory Committee."	To include the process of SAE review.
90-93	Appendix B: Replaced old Study Proposal Form with revised Concept Sheet Submission Form.	To clarify the title and use of the Concept Sheet Submission Form.
95	Appendix D. Study Timeline Modified/Updated	To provide updated information relating to the Study Timeline.

ADDITIONAL CONSENT FORM CHANGES

Included with these changes are minor administrative and grammatical changes.
Recommended change (Include sentence in the blood draw section of your consent form): "If we are unable to obtain a blood sample a repeat sample may be collected or you may be asked to reschedule the study visit."
Recommended change (Include sentence in the psychological testing section of your consent form): "We will use some psychological surveys and tests to learn about your child's thoughts, feelings, behaviors and cognitive (thinking) abilities."
Suggested change (check your local IRB requirements): "Children who turn 18 years old before the end of the study will be re-consented."

January 2007 Amendment (Amendment 3): CKiD Protocol Amendment Table-lists the changes from 01/01/06 version of the protocol to 01/01/07

1, 11, 27, 28, 29, 30, 37, 38, 39, 40, 41, 71, 74, 85	Deleted HPLC throughout the protocol and from Diagram 5.4.1 and Table 5.4.2a.	The CBL has discontinued performing HPLC.
9	Changed the number of clinical sites from “54” to “51”	To document the reduction in number of participating sites.
10	<p>The following site Principal Investigators were changed:</p> <ul style="list-style-type: none"> • Replaced Barry Warshaw with Larry Greenbaum at Children’s Healthcare of Atlanta at Egleston, Emory University • Replaced Larry Greenbam with Cynthia Pan at the Medical College of Wisconsin • Replaced Robert Mak with Amira Al-Uzri, MD at Oregon Health Science University • Replaced Peter Yorgin with Cynthia Wong at Stanford Univ. <p>Deleted the following Mid West sites:</p> <ul style="list-style-type: none"> • Children’s Hospital Central California • Hospital Infantil de Mexico <p>Added the following Mid West site:</p> <ul style="list-style-type: none"> • Children’s Kidney Specialist – Idaho (PI: Randall Jenkins, MD) <p>Renamed “Emmanuel Children’s Hospital” to “Northwest Pediatric Kidney Specialists”</p>	<p>To document a change in the Site Principal Investigator</p> <p>To remove the sites that are no longer participating in CKiD</p> <p>To include the new participating CKiD sites</p> <p>To document the renaming of an existing site</p>
11	<p>Deleted the following East Coast sites:</p> <ul style="list-style-type: none"> • Alfred I. DuPont Hospital • Nemours Children’s Clinic • North Shore University Hospital and Schneider Children’s Hospital, Long Island Jewish • Vanderbilt Children’s Hospital <p>Added the following East Coast sites:</p> <ul style="list-style-type: none"> • Carolina Medical Center 	<p>To remove the sites that are no longer participating in CKiD</p> <p>To include the new participating CKiD sites</p>

	<ul style="list-style-type: none"> DeVos Children’s Hospital at Spectrum Renamed “New York Presbyterian Hospital” to “Weill Medical College of Cornell University” 	To document the renaming of an existing site.
11, 42, 87	Changed the procedure for obtaining Lab Results. Protocol changed to “Laboratory results will be available on NEPHRON, the data management system for the CKiD study. NEPHRON is located at https://statepiaps.jhsph.edu/nephron/groups/aspproc/ .”	To inform sites that laboratory results will only be available electronically.
13	Added Paula Maier, George Schwartz and Alicia Wentz to Steering Committee.	To document the new Steering Committee members
19, 20, 22, 23, 24, 25, 28	Increased eligibility criteria using the Schwartz GFR from 75 to 90.	To provide broader eligibility inclusion and facilitate recruitment
19	Updated Recruitment Goal	To provide consistency with increasing sGFR to 90.
23, 24, 25	Updated SCr tables 5.2.1a, 5.2.1b and 5.2.1c	To provide consistency with increasing sGFR to 90.
25	Changed wording to indicate that families may receive meal vouchers and children may receive a small gift.	To provide sites with the flexibility of providing additional incentives.
26	<p>Added information regarding the timeline for scheduling study visits. Added “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 12 months after the eligibility form is completed. V1b will be scheduled within 6 months but no more than 12 months after V1a. The subsequent follow-up visits will be scheduled as follows:</p> <ul style="list-style-type: none"> the first annual follow-up visit (V2) will occur 12 months after V1a, plus or minus one month. However, if the visit is difficult to schedule, the visit can also be scheduled no more than 24 months after V1a. Visit 3 will be scheduled 24 months (\pm one month) after V1a or no more than 36 months after V1a for visits that are difficult to schedule. Visit 4 will be scheduled 36 months (\pm one month) after V1a or no more than 48 months after V1a for visits that are difficult to schedule.” 	To provide more flexibility in scheduling study visits.

26	Added information regarding when ECHO, ABPM, Cognitive studies can be conducted. Added “If the ECHO, Ambulatory Blood Pressure Monitoring (ABPM) and Neurocognitive testing data can not be obtained during the child’s scheduled study visit, these measurements will be scheduled within ± one month of the scheduled visit.”	To provide more flexibility in scheduling study visits.
27	Added information regarding rescheduling study visits. Added “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.”	To provide more flexibility in scheduling study visits.
29, 62, 68, 88	Changed the information about bone biopsies to note that biopsies will not be performed during CKiD visit, but a subset of children who have bone biopsies performed at UCLA will have data included in CKiD database. Added “Data generated from a small subset of children undergoing bone biopsies at University of California – Los Angeles plus or minus (±) six months will be incorporated in the CKiD database.”	To document the change in the bone biopsy protocol. Specifically, bone biopsy procedure will not be performed but data collected on a subset of children at UCLA will be included in CKiD database.
30	Updated Table 5.4.2a – added local renal panel, removed Tanner Staging at V1b, added Food Frequency Questionnaire, removed Diet History, and revised footnotes to state “Clinical sites will perform renal panel tests at their local laboratory for all participants in addition to the central renal panel tests that are sent to CBL” and “Clinical sites that require immediate results will perform urine creatinine and urine protein tests at their local laboratory in addition to the tests that are sent to CBL”, and revised Bone Biopsy footnote to state that “Bone Biopsy data for children undergoing bone biopsies at UCLA will be included in database.”	To document the changes in measurements
30, 35, 59, 61	Added Food Frequency to list of questionnaire completed during V1b and subsequent follow-up visits.	To provide an instrument to obtain dietary information at the study visit.

31	Added “If inadequate samples are collected at V1b, then additional whole blood will be collected and shipped at V3 or a future study visit.”	To provide documentation of the specific visit in which additional blood for the Genetic Repository will be collected in the event that cell lines and DNA samples can not be immortalized from the initial V1b blood collected.
31	Added “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.”	To provide an opportunity to collect the samples at a future study visit.
32	Updated Figure 5.4.2c – reduced the number children in which bone biopsy data will be collected from 20 to 10, and changed the frequency to only once.	To document the change in the bone biopsy protocol. Specifically, bone biopsies will not be performed but data collected on a subset of children at UCLA will be included in CKiD database.
33, 40	Changed the Schwartz GFR (sGFR) trigger and timeline for Accelerated study visits from $sGFR \leq 15$ and visit within 3 months to $sGFR \leq 20$ within 6 months.	To provide earlier detection of kidney disease decline so a study visit can occur before the participant progresses to ESRD and to provide more flexibility when scheduling the accelerated study visit.
34	Added “Tanner staging will be performed at the first component of the baseline visit (V1a) and not repeated at the second baseline component (V1b).”	To eliminate the need for obtaining information that is unlikely to change from V1a to V1b.
35	Deleted to “CKiD calendars will be sent home with patients at annual visits to track hospitalizations and their reasons.”	Sites are not required to provide calendars to families.
35, 59, 60	Removed Three Day Diet History	To document the change in protocol in which three day diet history will not be collected.
37	Added “If collected blood is grossly hemolyzed, additional blood may be collected during the study visit.”	To provide the ability to collect another sample for grossly hemolyzed.

39	Added “(or any acceptable vascular access can be used)” and removed “Provider should use acceptable vascular access.”	To provide an alternate method for collecting blood and maintain consistency with Manual of Procedures.
39	Increased Make-up GFR visit window – from “within one month” to “within 3 months”	To provide more flexibility in scheduling Make-up GFR study visits.
41	Deleted information that stated sample could be collected “in any clean container” and “Samples collected at home will be transferred into a urine collection tube at the clinical site.”	To document the change in the protocol.
41	Update information in Sections 6.2.1.6, 6.2.1.8, 6.2.1.9 and 6.2.1.10 to indicate that measures will be run at the local laboratories.	To document the change in protocol in which a local renal panel will be performed on all study participants.
42	Changed title and information in section 6.2.12. Title changed to “Tests Performed Locally.” Revised the text as follows, “In addition to the samples sent to the Central Biochemistry Laboratory, a renal panel will be performed locally for all study participants. The renal panel consists of a basic metabolic panel, phosphorous and albumin tests. Also, if lab results are needed immediately for clinical care, then 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://statepiaps.jhsph.edu/nephron/groups/aspproc/ .”	To document the change in protocol in which a local renal panel will be performed on all study participants.
53	Changed “26-hour to 24-hour.” Sentences changed to “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.”	To document the decision made by the ABPM Lab to monitor BP over a 24 hour period instead of 26 hour recording. Change consistent with information in revised MOP.
54	Deleted “ECHO results will be sent back by ID to the local centers for study participants and their physicians.”	To document that ECHO results will not be provided to clinical sites.

55	Added “However, in the event that a clinical site’s 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).”	To facilitate the completion of V2 study visits for sites that have not received ECHO certification so that retention is not compromised.
60	Renamed assay used to measure iPTH to “The ADVIA Centaur Intact PTH assay is a two-site sandwich immunoassay using direct chemiluminometric technology”	To document the new assay used to measure iPTH.
63	Deleted “in the opposite antecubital vein and closing it to a "heparin lock”	To document that heparin lock is not always used.
64	Change wording for vein access to “Acceptable vascular access should be used” and “Provider should use acceptable vascular access.”	To provide an alternate method for collecting blood and maintain consistency with Manual of Procedures.
85	Added “ECHO Alert parameters include findings of congenital disease, vegetation, tumor, pericardial effusion and/or tamponade, left ventricular or atrial thrombus, or cardiomyopathy (hypertrophic/dilated). It will be the responsibility of the local site to 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. In instances in which an “alert” parameter is identified up by the Cardiovascular Imaging Core Research Laboratory (CICRL), the alert will be reported on the website ECHO Report as “ALERT Found.” Otherwise “No Alert” will be indicated on the ECHO Report. For instances in which an alert is found, (the same process as indicated above should be followed) the CICRL will contact the site PI. In addition, the PI will then be responsible for contacting the Primary Nephrologist.”	To document the procedure for handling ECHO alert findings.
86	Changed “Urgent Alert” to “Significantly Abnormal Results.” Added “In addition to centrally performed renal panels, clinical sites will perform local BMP for all study participants. Therefore for certain	To document the procedure for following up with children with significantly abnormal results.

	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.	
91	<p>Updated the Subcommittee Lists</p> <ul style="list-style-type: none"> • Added Guillermo Hidalgo, Christopher Pierce and Vikas Dharnidika to Kidney Disease Subcommittee • Added Debbie Gipson and Alicia Wentz to Neurocognitive Subcommittee • Added Juan Kupferman to Cardiovascular Subcommittee • Added Hilary Hotchkiss to Growth Subcommittee • Added Alicia Wentz to Data Management, Analysis and Quality Control Working Group • Added Patrick Brophy and Victoria Norwood to Laboratory Working Group 	To document new members to each committee.
95	Replaced Judy Konig with Judith Jerry-Fluker	To document change in personnel.
98	Update the study timeline to reflect the accomplishments made since last amendment and the extension of enrollment.	To document the accomplishments and enrollment period.

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	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.	
91	<p>Updated the Subcommittee Lists</p> <ul style="list-style-type: none"> • Added Guillermo Hidalgo, Christopher Pierce and Vikas Dharnidika to Kidney Disease Subcommittee • Added Debbie Gipson and Alicia Wentz to Neurocognitive Subcommittee • Added Juan Kupferman to Cardiovascular Subcommittee • Added Hilary Hotchkiss to Growth Subcommittee • Added Alicia Wentz to Data Management, Analysis and Quality Control Working Group • Added Patrick Brophy and Victoria Norwood to Laboratory Working Group 	To document new members to each committee.
95	Replaced Judy Konig with Judith Jerry-Fluker	To document change in personnel.
98	Update the study timeline to reflect the accomplishments made since last amendment and the extension of enrollment.	To document the accomplishments and enrollment period.

11	Removed Stephen Cole as a co-investigator at the Data Coordinating Center.	To remove an investigator that is no longer participating in CKiD at the Data Coordinating Center
11	Protocol changed such that cystatin C will be shipped to Central Biochemistry Laboratory for all annual visits.	To document Steering Committee's decision to the change the location where cystatin C is shipped
11,35	Added "iron" measured centrally.	To document Steering Committee's decision to perform iron at the CBL starting at all visits
11,35	Added "uric acid" measured centrally.	To document Steering Committee's decision to measure uric acid at the CBL starting at Visit 4
11,35	Added "urine albumin" measured centrally.	To document Steering Committee's decision to perform microalbuminuria at the CBL starting at all visits
12, 29	Added "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 the next study visit."	To document Steering Committee's decision to obtain additional toe nail samples at Visit 4
13	Removed Anne Carlson and Stephen Cole from Steering Committee. Added Alison Abrahm, Silvia Cohn, Joseph Flynn, Arlene Gerson, Larry Greenbaum, Stephen Hooper, Mark Mitsnefes, Jacqueline Ndirangu, Christopher Pierce and Christine Smith to Steering Committee.	To document the old and new Steering Committee members
19	Changed Table 4.2 and all pertinent information describing the table. The table and information indicates the number of children enrolled as opposed to the targeted number.	To provide descriptive statistics of the children enrolled
21	Added "Currently, the cohort is comprised of a 15% African-American population. After reaching our original recruitment goal of 540 children, we will recruit an additional 60 African-American children, which will result in a racial demographic of 24%. To accomplish this goal of recruiting more African-American children, we will target recruitment at a selected number of sites located in geographical areas with high percentages of minorities (i.e., Washington, DC, Brooklyn, NY, and Chicago IL) and we will encourage sites to recruit minorities during Steering Committee and coordinator conference calls."	To document Steering Committee's decision to extend enrollment in order to facilitate the inclusion of additional African-American children in the cohort

26	Deleted “birthday cards.”	To correct error stated in previous version of protocol
26, 27	Increased enrollment period from two years to three years.	To provide more flexibility in accomplishing recruitment goal
27 – 30	Removed all references to contact pattern and cohort of first 270 and second 270. Removed Diagram 5.4.1 and Figure 5.4.2c.	To clarify the fact that there is only one cohort
28	Increased follow-up period from up to four years to “up to four years for CKiD I and up to an additional four years for CKiD II.”	To document Steering Committee’s decisions to continue to follow participants in CKiD II.
28	Updated Table 5.4.1a	To document Steering Committee’s decisions to add measurements obtained in CKiD II
30	Updated Table 5.4.1b	To document Steering Committee’s decisions to add measurements obtained in CKiD II
31	Changed accelerated study visit protocol. New protocol indicates that visits are triggered by children who are scheduled to have renal replacement therapy.	To provide more accuracy when identifying children who should be scheduled for accelerated study visits
32,57	Added the measurement of waist and hip circumferences starting at all visits.	Growth Subcommittee recommendation
38	Added information to justify changing the iohexol protocol at Visit 4 from 4 points to 3 points. Added “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-Mortensen equation, the GFR2 is calculated as $1.00959 \times \text{slowGFR} - 0.00139 \times \text{slowGFR}^2$. The excellent agreement ($r= 1$) of iGFR based on 4 points with iGFR2 based on 2 points provides support for simplifying the iohexol protocol. Therefore, starting at Visit 4, the number of blood draws will be reduced. To be conservative, the number of blood draws will be reduced to 3 time points, 120, 240 and 300 minutes. The collection of blood samples at three, rather than two points will offer several advantages. It will simplify the procedure; it will	To provide justification for changing iohexol protocol at Visit 4

	provide three points to estimate the slow curve of the log transformed concentrations; and it will also allow investigators in CKID II to compare the estimation of GFR using 120&300 minutes with 120&240 minutes data points. Hence, the agreement between the estimates may offer the possibility of shortening the overall measurement time from 300 to 240 minutes.”	
38	Removed all reference to obtaining a repeat measure for children with GFR less than to 20 ml/min 1.73m ² .	To document Steering Committee’s decision
39	Reworded the information regarding the timeline in which Cystatin C is obtained. Revised sentence reads, “We will include each of these measurements at baseline and at all annual study visits.”	To document Steering Committee’s decision to obtain cystatin C at all annual visits
39	Added “Most uric acid is filtered by the kidneys and passes out of the body in urine. However, if too much uric acid is produced or if the kidneys are unable to remove it from the blood normally, then the level of uric acid in the blood increases. Starting at Visit 4 and at all annual visits, we will measure uric acid centrally.”	To document Steering Committee’s decision to measure uric acid
40	Added “Using the first morning urine that is sent centrally, we will measure urinary albumin at baseline and at all annual study visits.”	To document Steering Committee’s decision to measure microalbuminuria
40	Reworded the information regarding timeline in which serum albumin is obtained. Serum albumin will be measured by the central and local laboratories at baseline and at all annual visits.	To correct error stated in previous version of protocol
40	Added “Iron deficiency in children with kidney disease is common. Iron will be measured by the central laboratory at baseline and at all annual visits.	To document Steering Committee’s decision to measure iron
42,44-48	Made grammatically changes and added three assessments to neuropsychological-battery: DKEF-Tower, WISC-IV Digit Span and WAIS-III Digit Span Subtests.	Neurocognitive Subcommittee recommendation
45,46	Removed three behavioral assessments: ABAS, BASC-SRP and CDI	Neurocognitive Subcommittee recommendation
43,45	Updated Diagrams 6.3.1.1 and 6.3.1.2 with the changes to the neuropsychological and behavioral batteries.	To illustrate the Neurocognitive Subcommittee recommendations
48	Removed “three” from selected sites conducting non-core neurocognitive testing.	To provide the flexibility of having an unspecified number of clinical sites conducting non-core neurocognitive testing

48	For neuroimaging study, changed the measurement used to identify children eligible for participation. Change measurement from estimated GFR to iohexol GFR.	To document the changes in GFR measurements
49	Separate Benton test into categories: Benton Form Discrimination and Benton Judgment of Line Orientation	Neurocognitive Subcommittee recommendation
50	Revised Neuroimaging protocol	Neurocognitive Subcommittee recommendation
57,58	Added the measurement of Vitamin D at baseline and every other year thereafter (i.e., V1b, V3 etc.)	To document Steering Committee's decision to measure vitamin D
57,58	Added the collection of subjective global assessment data at Visit 4 and at subsequent annual visits.	Growth Subcommittee recommendation
58	Added whole body DEXA scan and bone aging will be performed at selected sites starting at Visit 3.	Growth Subcommittee recommendation
64,65,73	Removed references to "3 day diet history"	To provide consistency with Steering Committee's decision to no longer collect 3 day diet history
78	Removed references to sites visits and quarterly conference calls with principal investigators and coordinators.	To provide consistency with budget because funding does not allow for site visits and quarterly conference calls
78	Changed "Monthly Steering Committee calls" to "Bi-monthly Steering Committee conference calls."	To provide consistency with study practice because implementation of procedures warrants more frequently conference calls among Steering Committee members
78,79	Added "Annual Investigator/Coordinator" Meetings and revised the meeting agenda	To provide a description of the current meeting agenda
83	Reworded two sentences regarding the transmission of study findings. Sentences read "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."	To describe the current process for transmitting information to sites
88	Removed Data Management, Analyses and Quality Control Subcommittee, Laboratory/Specimen Working Group and Training and Educations/Recruitment and Retention Subcommittee.	To document change in structure of subcommittees/working groups

88	<p>Updated the Subcommittee Lists</p> <ul style="list-style-type: none"> • Added Christopher Cox and Colin White to Kidney Disease Subcommittee • Removed Stephen Cole from Kidney Disease Subcommittee • Replaced Shlomo Shinnar with Stephen Hooper and Arlene Gerson as Neurcognitive Subcommittee Co-Chairs (Shlomo Shinnar remains a member of subcommittee) • Added Mina Matsuda-Abedini to Neurocognitive Subcommittee • Removed Ron Portman from to Cardiovascular Subcommittee • Added Silvia Cohn, Victoria Pemberton, Christopher Pierce and Joshua Samuels to Cardiovascular Subcommittee • Removed Stephen Cole and Haitao Chu from Growth Subcommittee • Added Alison Abraham to Growth Subcommittee 	To document new members to each committee and the removal of individual no longer participating on each subcommittee
95	Update the study timeline to reflect the accomplishments made since last amendment and the extension of enrollment.	To document the accomplishments and enrollment period

July 2008 Amendment (Amendment 4): CKiD Protocol Amendment Table-lists the changes from 04/15/08 version of the protocol to 07/01/08

44	Added neuropsychological assessment: WAIS-IV Digit Span Subtest.	Neurocognitive Subcommittee recommendation
44	Removed neuropsychological assessment: WIAT-II-A	Neurocognitive Subcommittee recommendation

December 2009 Amendment (Amendment 5): CKiD Protocol Amendment Table-lists the changes from 07/01/08 version of the protocol to 12/01/09

Cover page	Added Central Biochemistry Laboratory’s Address	To provide the official mailing address for the CBL
9	Change the number of participating clinical sites from “50” to “47.”	To reflect the number of participating clinical sites documented in Tables 3.2.1 and 3.2.2
10	<p>The following site Principal Investigators were changed:</p> <ul style="list-style-type: none"> • Replaced Fred Strife with Jens Goebel at Children’s Hospital and Medical Center, Cincinnati <p>Deleted the following Midwest site:</p> <ul style="list-style-type: none"> • Children’s Hospital of Los Angeles <p>Renamed:</p> <ul style="list-style-type: none"> • “Children’s Healthcare of Atlanta at Egleston, Emory University” to “Egleston Children’s Hospital, Emory University” • “Children’s Hospital and Medical Center – Cincinnati” to “Cincinnati Children’s Hospital and Medical Center” • “Oregon Health Science University” to “Oregon Health and Science University” • “UCSF Children’s Renal Center” to “UCSF Children’s Hospital” • “University of New Mexico” to “University of New Mexico Children’s Hospital” • “Children’s Medical Center Dallas” to “University of Texas Southwestern Medical Center” 	<p>To document a change in the Site Principal Investigator</p> <p>To document removal of the site that is no longer participating in CKiD</p> <p>To document the renaming of an existing site</p>
11	<p>The following site Principal Investigators were changed:</p> <ul style="list-style-type: none"> • Removed Hilary Hotchkiss from Robert Wood Johnson Medical School – UMDNJ • Replaced Lynne Yao with Lauren Weintraub at INOVA Fairfax Hospital for Children • Replaced Debbie Gibson with Maria Ferris at University of North Carolina, Chapel Hill <p>Deleted the following East coast sites:</p> <ul style="list-style-type: none"> • State University of New York Downstate Medical Center 	<p>To document a change in the Site Principal Investigator</p> <p>To document removal of the sites that are no longer participating in CKiD</p>

	<ul style="list-style-type: none"> Weill Medical College of Cornell University 	
13	Removed Silvia Cohn, Emmeline Edwards, Nancy Fink, Barbara Fivush and Alicia Wentz from Steering Committee membership list.	To document the change in Steering Committee members
18	Under Study Acknowledgment section, added Central Biochemistry Laboratory.	To provide consistency with the information stated in the concept sheet submission form
19	Changed Table 4.2 and all pertinent information describing the table. The table and information indicates the number of children enrolled as opposed to the targeted number.	To provide descriptive statistics of the children enrolled
3, 19, 22, 26, 53, 72, 75, 76, 77	Changed the targeted enrollment number from 540 to approximately 600 throughout protocol.	To document the Steering Committee's decision to enroll an additional 60 children
21	Revised Section 4.2.3 "After reaching the original recruitment goal of 540 children, the cohort 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 22%. 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."	To document the current number of African-American children enrolled in the cohort
26	Changed number of years of follow-up in CKiD II from "four" to "an additional five years in CKiD II"	To accurately describe the possible number of follow-up years during CKiD II funding cycle
26	<p>Added visits 5 - 8 to follow-up visit schedule:</p> <ul style="list-style-type: none"> Visit 5 will be scheduled 48 months (\pm one month) after V1a or no more than 60 months after V1a for visits that are difficult to schedule. Visit 6 will be scheduled 60 months (\pm one month) after V1a or no more than 72 months after V1a for visits that are difficult to schedule. Visit 7 will be scheduled 72 months (\pm one month) after V1a or no more than 84 months after V1a for visits that are difficult to schedule. Visit 8 will be scheduled 84 months (\pm one month) after V1a or no more than 96 months after V1a for visits that are difficult to schedule 	To update the total number of visits and clarify the follow-up schedule for visits 5 – 8 which are to be completed during CKiD II i.e. the 2nd funding cycle of the grant
26, 27	Added additional information about the ABPM schedule "In the event that the ABPM device is not initiated within one month of the visit, the site should	To document Cardiovascular Subcommittee's recommendation to

	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 within one month of the scheduled visit, the site should contact their respective CCC for further instructions.”	encourage sites to obtain Mabis Medic auscultatory blood pressure measurements at the time the ABPM device is initiated
28	Removed “CKiD I” and “CKiD II” from table header.	To remove the distinction between CKiD I and CKiD II
30	Changed sentence and footnote below Table 5.4.1b. “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.”	To document that toenail clippings can be collected at a future CKiD visit.
31	Changed “accelerated” to “irregular” study visit protocol.	To provide consistency with Data Coordinating Center’s definition of the visit prior to renal replacement therapy
31	Added information about the phone/in-person follow-up protocol. Added “Participants will be given the option to participate in the follow-up protocol after they exit the study due to renal replacement therapy, pregnancy, loss to follow-up or withdrawal. The follow-up protocol will be composed of two components: an interview and chart review. For convenience, the follow-up interview will be completed over the phone or in-person. During the interview the study will obtain renal therapy status, sociodemographic information, medical history, health care utilization status, medication use, physical symptoms and quality of life data. In conjunction with the follow-up interview, the coordinator will collect data (i.e., lab results) from chart review to ascertain accurate data. The follow-up protocol will be scheduled to occur annually based on the anniversary date of the participant’s baseline (V1a) visit (\pm 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 will occur annually based on the anniversary baseline (V1a) date (\pm two months).”	To document the Steering Committee’s decision to add the phone follow-up protocol. Therefore, allowing the study to continue obtaining information on the health status and long-term outcomes of Chronic Kidney Disease among participants who exit the study prematurely
32	Added age requirement for head circumference, “Head circumference for children 3 years old and younger,…”	To provide clarity and consistency with other sections of the protocol

32	Added parental occupation and census block group as a type of sociodemographic information data collection.	To document the Steering Committee's decision to obtain additional measures to appropriately classify socioeconomic status (SES)
34	Added information about nail clippings and hair samples. "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."	To document that toenail clippings can be collected at a future CKiD visit
34	Added information about NHANES physical activity questions. Added "Physical activity questions adapted from the National Health and Nutrition Examination Survey (NHANES) will be collected for all participants 2 years and older."	To document Steering Committee's decision to obtain physical activity data for all participants 2 years and older using the NHANES physical activity questionnaire
41	Added information about the use of extra serum at the Central Biochemistry Laboratory. Added "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 and 1,25 vitamin D."	To document Steering Committee's decision to use left over serum as an alternative sample source for performing additional ancillary studies (pending additional funding)
42,43,45	Removed any reference to WAIS-III	WAIS-IV is widely distributed by manufacture so sites should discontinue using WAIS-III
42,45-47	Added three behavioral assessments for older study participants: <ul style="list-style-type: none"> • BASC-SRP to be completed by participants 21 to 25 years old • SF-36 to be completed by participants 18 years and older • BRIEF-A to be completed by participants 18 years and older 	To document the Neurocognitive Subcommittee's recommendation to provide additional age-appropriate behavioral assessments for older study participants who are transitioning into young adulthood
43	Updated Diagram 6.3.1.1 to illustrate the existing neuropsychological assessments completed by older children.	To illustrate the Neurocognitive Subcommittee recommendations
45	Updated Diagram 6.3.1.2 with the changes to the behavioral battery for older children.	To illustrate the Neurocognitive Subcommittee recommendations
88	Updated the Subcommittee Lists <ul style="list-style-type: none"> • Added Alison Abraham, Tom Blydt-Hansen and Marty Turman to Kidney Disease Subcommittee 	To document new members to each committee and the removal of

	<ul style="list-style-type: none"> • Removed Kathy Jabs, Alicia Neu and Mouin Seikaly from Kidney Disease Subcommittee • Added Alison Abraham and Matthew Matheson to Neurocognitive Subcommittee • Removed Ira Davis from Neurocognitive Subcommittee • Added Gina-Marie Barletta, Randy Jenkins, Jonathan Kaltman, Tammy Brady, Anil Mongia, Derek Ng, Tim Poffenbarger, Cynthia Wong and Ellen Woods to Cardiovascular Subcommittee • Removed Tom Blydt-Hansen, Silvia Cohn, Stephen Daniels and Marty Turman from to Cardiovascular Subcommittee • Added David Askenazi, Juhi Kumar, Matthew Matheson, Michael Schneider, George Schwartz and Ora Yadin to Growth Subcommittee • Removed Lynne Haverkos, Richard Fine and Valerie Johnson to Growth Subcommittee 	individual no longer participating on each subcommittee
89-92	Updated concept sheet submission form.	To document recommendations made by Steering Committee members to improve the form with updated information
95	Update the study timeline to reflect the accomplishments made since last amendment and the extension of enrollment.	To document the accomplishments and enrollment period

November 2010 Amendment (Amendment 6): CKiD Protocol Amendment Table-lists the changes from 12/01/09 version of the protocol to 11/01/10

Cover page	Changed the East Coast Coordinating Center’s Address	To reflect the transfer of the ECC from JHMI to CHOP
3	Changed expected number of Americans who will have ESRD from “650,000” to “785,000”	To reflect new 2020 prediction
9, 11, 18	Added the new location of East Coast Coordinating Center, “Children’s Hospital of Philadelphia.”	To reflect the transfer of the ECC from JHMI to CHOP
9	Changed number of clinical sites from 47 to 50	To reflect the addition of new CKiD sites
10	The following site Principal Investigators were changed: <ul style="list-style-type: none"> • Replaced Mark Benfield with Sahar Fathallah at Children’s Hospital of Alabama • Replaced Deborah Jones with Colleen Hastings at Lebonheur Children’s Medical Center • Replaced Beth Vogt with Katherine Dell at Rainbow Babies & Children’s Hospital 	To document changes in the site Principal Investigators
11	The following site Principal Investigators were changed: <ul style="list-style-type: none"> • Replaced Gina Barletta with Yi Cai • Replaced Susan Furth with Meredith Atkinson • Replaced Katherine Collins with Debbie Gipson <p>Added:</p> <ul style="list-style-type: none"> • “Children’s Hospital of Philadelphia” • “Hospital for Sick Children (Sick Kids)” • “University of Iowa” <p>Added:</p> <ul style="list-style-type: none"> • Susan Furth • Lisa Robinson • Patrick Brophy 	To document changes in the site Principal Investigator To document the addition of new sites To document the principal investigators at the additional new sites
11, 38	Changed “iron” to “iron studies”	To clarify that there are multiple tests performed to determine iron deficiency
11, 59, 60	Changed “wide range” to “high sensitive”	To document the change in test used to measure C-reactive protein

12	Changed sentence to state, “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 Cohort 2, cystatin C will be measured at the CBL.”	To document that baseline measurements for Cohort 2 will be performed at the CBL
12	Changed Montefiore Medical Center to Seattle’s Children Hospital	To reflect Joseph Flynn’s relocation from Montefiore to Seattle
12	Changed Montefiore Medical Center to University of North Carolina	To document the change in the central laboratory for MRI reading
12	Deleted “(N=30)”	To document the Neurocognitive Committee’s changes to the MRI protocol
19-23, 28, 29, 32, 40, 60	Updated information throughout regarding re-opening enrollment to include Cohort 2.	To document the Steering Committee decision to re-open enrollment and recruit children with non-glomerular and glomerular disease based on an eGFR of 45 to 90
19	Changed Table 4.2 and all pertinent information describing the table. The table and information includes the final number to be enrolled in Cohort 1.	To reflect the final number of children enrolled in cohort 1
20	Added information about the higher number of African-American children projected to be enrolled in Cohort 2. Added “In Cohort 1, 36% of children with glomerular disease were African-American. Since the study expects to enroll a higher proportion of children with glomerular disease, it is also expected that there will be more African-American children enrolled resulting in more generalizable study population.”	To document Steering Committee decision to increase enrollment among children with glomerular disease resulting in an increase in the number of African-American children enrolled
23	Added information about the cap which will be placed on enrolling children with non-glomerular disease. Added “In contrast to the recruitment efforts of Cohort 1 where 78% of the cohort had non-glomerular disease, the recruitment process of Cohort 2 will be focused on enrolling an equal distribution of children with glomerular and non-glomerular disease. Specifically, it is expected that 50% of the children in Cohort 2 will have glomerular disease and the study will place an upper limit of 60% for the percent of enrolled with non-glomerular disease. In the event that the upper limit is reached, sites will be notified that recruitment efforts should be focused on enrolling only children with glomerular disease.”	To document the Steering Committee’s decision to enroll an equal distribution of children glomerular and non-glomerular children (i.e., 140 with each)
27	Added Table 5.2.1d which provides the serum creatinine and height ranges for children eligible for Cohort 2.	To provide sites with a table to determine eligibility

28	Added “cancer/leukemia diagnosis or pregnancy” as additional reasons for disenrollment from the study	To document the Steering Committee’s decision to disenroll children with cancer/leukemia or who become pregnant
31	Updated Table 5.4.1a <ul style="list-style-type: none"> • Changed “iron” to “iron studies” • Deleted “Neuropsychological Assessments for High Risk Children” • Changed “Wide Range CRP” to “High Sensitive CRP” • Added “Fibroblast Growth Factor 23 (FGF-23)” • Listed the names of the iron tests performed 	To provide consistency with information presented throughout the protocol
32	Revised the sentence to state “The only limitation for the study is that for Cohort 2, half of the cohort will have only one assessment of cardiovascular risk factors during the funding cycle from 2008 to 2013.”	To describe that the limitation applies only to Cohort 2 during the funding cycle of CKiD II
34	Revised last sentence of the “irregular” study visit protocol to include the new projected number of active participants. “...it is projected that by the end of August 2013, only 47% of Cohort 1 will remain active.”	To provide more accurate information regarding the projected composition of cohort 1
34	Added information about children with cancer/leukemia to the phone/in-person follow-up protocol. “However, children who exit due to cancer/leukemia diagnosis will be ineligible to participate in the follow-up protocol.”	To document the Steering Committee’s that children with cancer/leukemia are ineligible for the phone/in-person follow-up protocol
37	Added “arsenic” to list of heavy metals.	To provide another type of heavy metal
37	Added information about health literacy and numeracy as another data collection tool. Added “The Short Test of Functional Health Literacy in Adults (STOFHLA), a standardized instrument, will be administered to parents/legal guardian (i.e., caregiver) of participants to assess health literacy. In the event that the participant attends the visit unoccupied by their parent, the participant will complete the assessment. For Cohort 1, the survey will be administered at the participant’s upcoming follow-up visit; however, for Cohort 2 it will be administered at the baseline visit. In addition, numeracy assesses an individual’s mastery of the basic symbols and processes of arithmetic. Using a standardized tool, when it is available, numeracy will also be assessed.”	To document the Steering Committee’s decision to obtain information about health literacy and numeracy
40	Deleted “...consistent with the United States Recommended Daily Allowance (USRDA) of protein.”	To provide clarification because children are not required to eat a low protein diet

40	Added information about 2-point GFR study, "... 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 $1.00959 \times \text{slowGFR} - 0.00139 \times \text{slowGFR}^2$. 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, the number of blood draws will be reduced to 2 time points (120 and 300)."	To document the Steering Committee decision to reduce the number for iohexol blood draws from 3 to 2.
41	Changed "4 blood samples" to "2 blood samples"	To document the Steering Committee decision to reduce the number for iohexol blood to 2.
41	Deleted information about 3-point protocol.	To document the Steering Committee decision to reduce the number for iohexol blood draws from 3 to 2.
41	Added "original" and "originally"	To document the differentiation between sGFR and eGFR
41	Added information about updated Schwartz formula used to estimate GFR in Cohort 2. Added "The Schwartz formula devised in the mid-1970s has recently 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 $0.413 \times (\text{height}/\text{serum creatinine})$, provides an updated Schwartz formula to estimate GFR."	To describe the updated Schwartz's equation
43	Changed "iron" to "iron studies" and listed the names of the iron tests performed	To clarify that multiple tests are performed as part

45, 48	Changed “Behavior Assessment System for Children – Self Report of Personality (BASC-SRP)” to “Behavior Assessment System for Children – Self Report of Personality, College Version (BASC-SRP COL)”	To document the Neurocognitive’s decision to administer the BASC-SRP College version to older participants
45, 48, 49	Changed “SF-36” to “PedsQL young adult version”	To document the Neurocognitive’s decision to administer the PedsQL young adult version to older participants instead of SF36
49	Deleted non-core “high risk battery”: <ul style="list-style-type: none"> • Delis-Kaplan Executive Function System (DKEFS) • Benton Form Discrimination (Benton-Form) • Benton Judgment of Line Orientation (Benton-Judgment) • Clinical Evaluation of Language Fundamentals – 4th Edition (CELF-4) 	To document the Neurocognitive Committee’s decision to remove the tests for at-risk children
49-52	Updated neuroimaging information	To document the Neurocognitive Committee’s changes to the MRI protocol
51	Deleted “In addition to examining overall IQ (WASI) from the core battery in relations to overall brain volume, we plan to explore the correlation between specific measures from the core and non-core battery for the at-risk children.”	To document the Neurocognitive Committee’s decision to remove the tests for at-risk children
52	Changed “Four BPs” to “Three BPs”, added “(unless there is a medical reason not to use it), and deleted “The first reading will be discarded and the average of the last three readings will be recording as the subject’s BP for that visit.”	To provide consistency with information provided in the Manual of Procedures and study forms
53, 54, 74	Changed “years 2 and 4 of the study” to “visit 2 and every other year thereafter	To allow for additional visits
54	Changed “Tapes” to “Videotapes/CDs”	To provide consistency with the information provided in Manual of Procedures and study forms
59-60	Added description of Fibroblast Growth Factor 23 (FGF-23)	To document the committee’s decision to measure FGF-23 centrally
77-78	Updated Section 9.1	To provide information on power calculations for Cohort 2
79	Changed “able to review a CKiD training DVD” with “trained at their clinical sites and/or by their respective CCC.”	To describe the training practice currently performed
79	Changed “annual” to “periodic”	To describe the process currently performed

79	Deleted “in the Washington, DC area”	To document the Steering Committee’s decision to conduct meetings to occur outside of the Washington DC area
85	Changed “medications” to “iohexol”	To clarify that iohexol is not used as a medication
87	Added “or designee”	To provide authorization for individuals other than the physician to review the study with the family
88	Changed “at study visits” to “within 24 hours of a study procedure”	To provide consistency with information provided in the Manual of Procedures and study forms
89	<p>Updated the Subcommittee Lists</p> <ul style="list-style-type: none"> • Removed Stanley Hellerstein from Kidney Disease Subcommittee • Add Katherine Dell to Kidney Disease Subcommittee • Add Jens Goebel to Kidney Disease Subcommittee • Add Susan Massengill to Kidney Disease Subcommittee • Add Craig Wong to Kidney Disease Subcommittee • Add Ryan Baer to Neurocognitive Subcommittee • Removed Victoria Pemberton from Cardiovascular Subcommittee • Add Lynn Weiss to Cardiovascular Subcommittee 	To document new members to each committee and the removal of individual no longer participating on each subcommittee
90-94	Updated concept sheet submission form.	To document new fees for shipping specimen for ancillary studies and
98	Update the study timeline to reflect the accomplishments made since last amendment and the extension of enrollment.	To document the accomplishments and enrollment period

September 2012 Amendment (Amendment 7): CKiD Protocol Amendment Table-lists the changes from 11/01/10 version of the protocol to 09/01/12

1, 9, 18	Removed the “National Institute of Neurological Disorders and Stroke (NINDS)”	To accurately list the NIH division that are providing funding
1, 9	Added “Central Biochemistry Laboratory”	To document the CBL as a separately funded entity
2	Added “end stage renal disease”	Grammatical correction
6	Removed comma after “and” so sentence reads “This study will ..., inflammation, and anemia) and medical management that...”	Grammatical correction
7	Added “growth hormone insulin like growth factor”	Grammatical correction
10	Added “Randall Jenkins” to Oregon Health and Science University Removed Northwest Pediatric Kidney Specialist Added: <ul style="list-style-type: none"> • “Vanderbilt University Medical Center” Added: <ul style="list-style-type: none"> • Deborah Jones 	To document a new site Principal Investigator at an existing site To document the removal of a non-participating site To document the addition of new sites To document the principal investigator at the new site
11	Changed “Children’s Memorial Hospital, Northwestern University” to “Ann & Robert H. Lurie Children’s Hospital of Chicago” The following site Principal Investigators (PI) were changed: <ul style="list-style-type: none"> • Added Rulan Parekh as a PI for Hospital for Sick Children • Replaced Mark Mentser with Hiren Patel • Replaced Vikas Dharnidharka with Richard Neiberger • Replaced Guillermo Hidalgo with Eunice John • Replaced Robert Weiss with Dmitry Samsonov Added: <ul style="list-style-type: none"> • “East Carolina University” • “State University of New York Downstate Medical Center” 	To document the hospital’s name change To document changes in the site Principal Investigator To document the addition of new sites

	<ul style="list-style-type: none"> • “Texas Children’s Hospital” <p>Added:</p> <ul style="list-style-type: none"> • Guillermo Hidalgo • Anil Mongia • Poyyapakkam Srivaths <p>Changed Site 85 to Site 65</p>	<p>To document the principal investigators at the additional new sites</p> <p>To reflect the correct site number for University of Iowa</p>
12	Changed the wording to, “In addition, University of North Carolina (affiliated with the east coast CCC) was the central laboratory for the magnetic resonance imaging (MRI) that was done in a small subset of the cohort. The University of North Carolina also coordinated central reading of the neurocognitive tests.”	To document the completion of the MRI sub-study
11,38,43	Removed “iron studies”	To document the Steering Committee decision to discontinue measuring iron studies
13, 98, 99, footer	Changed “External Advisory Committee (EAC)” to “Observational Study Monitoring Board (OSMB)”	To document the new name of the NIDDK advisory representatives
18	Removed “(Principal Investigator)” and reorganized grant numbers	To clarify that the numbers represent the grant number for the CCCs, DCC and CBL not the funding institutes
21, 28, 34	Removed “leukemia”	To provide clarification because leukemia is a form of cancer it is unnecessary to state it
28	Changed “Holiday cards will ...” to “Holiday cards may ...”	To allow the option for sites to send holiday cards
29	Added “and so forth”	To document that visits will continue until grant funding ends
30	Changed “(V1)” to “(V1b)”	Grammatical correction

31	<p>Updated Table 5.4.1a and footnote (if appropriate)</p> <ul style="list-style-type: none"> • Combined “Study Brochure” with “Consent Form” • Deleted “Iron Studies” • Combined “Central Urine Creatinine” and “Central Urine Protein” • Added “Pulse Wave Velocity” • Added “Cardiac Magnetic Resonance Imaging (MRI)” • Deleted “Neurocognitive Magnetic Resonance Imaging (MRI)” • Combined “Height/Length” and “Weight” • Added “6 Minute Walk Test (6MWT)” • Added “Grip Strength” • Deleted “DEXA Scan/Bone Age” • Deleted “Subjective Global Assessment” 	To provide consistency with information presented throughout the protocol
34	<p>Changed sentence about irregular visits to, “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...”</p>	To document the Steering Committee decision to obtain irregular visit data on children who transition to adult care/age-out or are unable to return to participating site for regular visits
34	<p>Changed sentence about irregular visits to, “For children requiring an irregular study visit, the irregular visit will be their last CKiD study visit prior to beginning the Phone/In-Person 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.</p>	To provide clarification that an irregular visit will not be the last CKiD visit instead participants will transition to the Phone/In-Person Follow-up interviews
34	<p>Revised sentence about phone/in-person follow-up protocol. Changed sentence to, “Participants will be given the option to participate in the phone/in-person follow-up protocol after they have renal replacement therapy, pregnancy, loss to follow-up or withdrawal. However, children who have a cancer diagnosis will be ineligible to participate in the follow-up protocol.”</p>	To provide clarification that individuals who have renal replacement therapy are not exiting the study but phone/in-person follow-up data can be collected
35	<p>Changed “describe” to “described”</p>	Grammatical correction

38, 44	Added “Beta-Trace Protein”	To document the Steering Committee decision to measure Beta-Trace Protein
44	Added “FGF-23”	To provide consistency with information presented throughout about FGF-23
45-50	<p>Updated neurocognitive battery</p> <ul style="list-style-type: none"> • Added “Second Edition” to WASI • Added additional DKEF subtests <ul style="list-style-type: none"> ○ Verbal Fluency Subtest ○ Figural Fluency Subtest ○ Color Word Interference Subtest • Added WISC-IV Spatial Span • Added Wechsler Memory Scale Third Edition (WMS III) Spatial Span • Deleted the non-core neuroimaging tests 	To document the Neurocognitive subcommittee decision to modify the battery of neurocognitive tests
57	Added description of “Pulse Wave Velocity” at selected sites	To document the Steering Committee decision to perform pulse wave velocity on sub-group of participants
57	Added description of “Cardiac MRI” to be performed for on sub-set of children with high probability of reaching ESRD	To document the Steering Committee decision to perform cardiac MRI at irregular visits
59, 60, 61	Added “6 Minute Walk Test” to list of core growth measurements and provided description of test	To document the Steering Committee decision to perform the 6 minute walk test
59, 60, 61	Added “Grip Strength Test” to list of core growth measurements and provided description of test	To document the Steering Committee decision to perform grip strength test
59,61	Deleted “Subjective Global Assessment” from list of core growth measurements and added description of “Subjective Global Assessment” as a non-core test	To document the Steering Committee decision to perform subjective global assessment on a sub-cohort of participants who begin dialysis treatment

60	Revised sentence about the frequency of obtaining FGF-23 measurement. Changed the sentence to, “FGF-23 will be measured centrally at baseline and then every other year thereafter.”	To provide consistency with information presented throughout about FGF-23
61	Deleted description of DEXA scans and Bone Age	To document the Steering Committee decision to remove DEXA from the protocol
80	Changed “sites” to “site”	Grammatical correction
87	Changed sentence about possible risk associated with blood draw to, “Drawing blood or inserting an IV catheter may cause faintness, inflammation of the vein, pain, bruising, infection or bleeding at the puncture site.”	To provide clarification
87	Added description of possible risk associated with pulse wave velocity	To provide possible risk associated with performing the pulse wave velocity procedure
87	Added description of possible risk associated with cardiac MRI	To provide possible risk associated with performing the cardiac MRI
88	Added sentence indicating no risk associated with performing 6 minute walk test	To document that there are no known risk associated with performing the 6 minute walk test
88	Added sentence indicating no risk associated with performing grip strength test	To document that there are no known risk associated with performing the grip strength
88	Removed “they” so sentence reads “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.”	Grammatical correction
88	Changed “HIPPA” to “HIPAA”	Grammatical correction
89	Added “(i.e., increased heart rate or blood pressure)”	To provide consistency with information reported in the adverse event report for outcomes that are anticipated as well as unanticipated

91	<p>Updated the Subcommittee Lists</p> <ul style="list-style-type: none"> • Changes to Steering Committee <ul style="list-style-type: none"> ○ Added Malot Minnick-Belarmino ○ Removed Shlomo Shinnar • Changes to Kidney Disease Subcommittee <ul style="list-style-type: none"> ○ Added Meredith Atkinson ○ Added Yi Cai ○ Added Larry Copelovitch ○ Added Sahar Fathallah ○ Added Gloria Williams ○ Replaced Robert Weiss with Dmitry Samsonov • Changes to Neurocognitive Subcommittee <ul style="list-style-type: none"> ○ Removed Ryan Baer ○ Removed Emmeline Edwards • Changes to Cardiovascular Subcommittee <ul style="list-style-type: none"> ○ Added Kristin Burns ○ Added Janis Dionne ○ Added Lisa Friedman ○ Added John Jefferies ○ Added Hiren Patel ○ Added Jack Weaver ○ Removed Randy Jenkins ○ Removed Lynn Weiss ○ Removed Ellen Woods • Changes to Growth Subcommittee <ul style="list-style-type: none"> ○ Added Amira Al-Uzri ○ Added Kanwel Kher ○ Added Kelly McDermott ○ Added Marva Moxey-Mims ○ Added Anthony Portale ○ Added Amy Skversky ○ Removed Kanwel Kher ○ Removed George Schwartz ○ Replaced Matthew Matheson with Lisa Friedman 	To document new members to each committee and the removal of individual no longer participating on each subcommittee
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93	Changed KIDMAC telephone number from 410-955-4320 to 410-614-1340	To provide the KIDMAC's new telephone number
100	Update the study timeline to reflect the accomplishments made since last amendment.	To document the milestones

July 2013 Amendment (Amendment 8): CKiD Protocol Amendment Table-lists the changes from 09/01/12 version of the protocol to 07/01/13

9	Updated Figure 3.2.1 and changed sentence to “The approximately 50 CKiD study sites are geographically shown in Figure 3.2.1.”	To document changes to the geographical location of clinical sites
10	<p>Removed “University of Wisconsin” and “LeBonheur Children’s Medical Center”</p> <p>Removed “Children’s Kidney Specialist – Idaho”</p> <p>The following site Principal Investigators (PI) were changed:</p> <ul style="list-style-type: none"> • Replaced Cynthia Wong with Paul Grimm 	<p>To document the removal of a non-participating sites</p> <p>To document that the removal of non-participating. Participants will be followed at Oregon Health and Science University</p> <p>To document changes in the site Principal Investigator</p>
11	<p>Ordered Table 3.2.2 in alphabetically and changed “Children Hospital of Michigan” to “Children’s Hospital of Michigan”</p> <p>Added:</p> <ul style="list-style-type: none"> • “Children’s Hospital of Richmond at Virginia Commonwealth University” <p>Added:</p> <ul style="list-style-type: none"> • Randala Lakkis <p>The following site Principal Investigator (PI) was changed:</p> <ul style="list-style-type: none"> • Replaced Lauren Weintraub with Patricia Seo-Mayer as PI for INOVA Fairfax Hospital for Children 	<p>To document grammatical changes</p> <p>To document the addition of new sites</p> <p>To document the principal investigators at the additional new sites</p> <p>To document change in the site Principal Investigator</p>
18	Added “(Principal Investigators)” to study acknowledgment statement.	Grammatical change
28	Increased follow-up period and changed sentence to “... up to 14 years in CKiD.”	To document the Steering Committee decision to follow participants in CKiD III

29	<p>Changed last bullet to “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.”</p>	To document that Vascular Test, cardiac MRI and Neurocognitive tests should be rescheduled if not performed during the study visit.
31	<p>Updated Table 5.4.1a and footnote (if appropriate)</p> <ul style="list-style-type: none"> • Added Visits 9 – 15 • Changed “Pulse Wave Velocity” to “Vascular Test” 	To document the Steering Committee decision to perform vascular tests instead of pulse wave velocity only on sub-group of participants and to follow participants in CKiD III
32	<p>Changed “2013” to “2018”</p>	To document the Steering Committee decision to follow participants in CKiD III
33	<p>Updated Table 5.4.1b</p> <ul style="list-style-type: none"> • Added Visits 9 – 15 	To document the Steering Committee decision to follow participants in CKiD III
34	<p>Changed “Phone/In-Person Follow-up” to “Continued Follow-up” and appropriately revised the paragraph to include “on-line” and “mail” as options for continued follow-up.</p>	To document the Steering Committee decision to use other options to collect follow-up data
37	<p>Changed description of Health Literacy and Numeracy tool to “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. For Cohort 1, the survey will be administered at the participant’s upcoming follow-up visit; however, for Cohort 2 it will be administered at the baseline visit or follow-up visit. In addition, numeracy assesses an individual’s mastery of the basic symbols and processes of arithmetic.”</p>	To provide clarification

41	<p>Added “cystatin C” and changed last sentences of make-up GFR description to “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.</p> <p>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.”</p>	To provide clarification
45, 47, 48	<p>Updated neurocognitive battery</p> <ul style="list-style-type: none"> • Changed WISC-IV Spatial Span to WISC-IV-I Spatial Span • Modified description of WASI II 	To clarify the difference between the WISC-IV and WISC-IV-I, and the description of the WASI II neurocognitive tests
57-58	<p>Changed “Pulse Wave Velocity” to “Vascular Test” and appropriately changed the paragraph to provide a description of the vascular tests.</p>	To document the Steering Committee decision to perform vascular tests instead of pulse wave velocity only on sub-group of participants
61	<p>Updated description of 6 Minute Walk Test</p>	To provide additional information regarding where the test can be performed and xxx measuring leg length
71-76	<p>Updated the study’s analytical plan</p>	To describe other analytical methods
89	<p>Changed “Pulse Wave Velocity” to “Vascular Test”</p>	To document the Steering Committee decision to perform vascular tests instead of pulse wave velocity only on sub-group of participants
90	<p>Removed underlining</p>	Grammatical change

93	<p>Updated the Subcommittee Lists</p> <ul style="list-style-type: none"> • Changes to Kidney Disease Subcommittee <ul style="list-style-type: none"> ○ Added Randala Lakkis • Changes to Neurocognitive Subcommittee <ul style="list-style-type: none"> ○ Replaced Robert Butler with Rebecca Johnson ○ Added Victoria Norwood ○ Added Patricia Seo-Mayer • Changes to Cardiovascular Subcommittee <ul style="list-style-type: none"> ○ Added Eunice John ○ Added Rulan Parekh ○ Added Amy Wilson • Changes to Growth Subcommittee <ul style="list-style-type: none"> ○ Added Eunice John ○ Added Cynthia Pan ○ Added Poyyapakkam Srivaths ○ Added Patricia Seo-Mayer 	To document new members to each committee and the removal of individuals no longer participating on each subcommittee
102	Update the study timeline to reflect the milestones made since last amendment.	To document the milestones
103, 105-107, 110 - 113, 115-117, 119-120	Updated references	To document new references and references that were removed

June 2014 Amendment (Amendment 9): CKiD Protocol Amendment Table-lists the changes from 07/01/13 version of the protocol to 06/01/14

10	<p>Changed “Rainbow Babies & Children’s Hospital” to “Case Western Reserve University”</p> <p>The following site Principal Investigator (PI) was changed:</p> <ul style="list-style-type: none"> • Replaced Paul Grimm with Cynthia Wong as PI for Stanford University Medical Center <p>Removed “Vanderbilt University Medical Center”</p>	<p>To document the site’s name change</p> <p>To document changes in the site Principal Investigator</p> <p>To document the removal of a non-participating site</p>
11	<p>Added:</p> <ul style="list-style-type: none"> • “Children’s Hospital at Dartmouth” <p>Added:</p> <ul style="list-style-type: none"> • Deborah Matossian <p>The following site Principal Investigator (PI) was changed:</p> <ul style="list-style-type: none"> • Replaced Richard Neiberger with Kiran Upadhyay as PI for University of Florida • Replace Randala Lakkis with Megan Lo at Children’s Hospital of Richmond At Virginia Commonwealth University <p>Changed “Jeffery Saland” to “Jeffrey Saland”</p> <p>Changed “UMDNJ-Robert Wood Johnson Medical School” to “RBHS-Robert Wood Johnson Medical School”</p> <p>Removed “State University of New York Downstate Medical Ctr”</p>	<p>To document the addition of a new site</p> <p>To document the principal investigators at the additional new site</p> <p>To document change in the site Principal Investigators</p> <p>Spelling correction</p> <p>To document the site’s name change</p> <p>To document the removal of a non-participating site</p>
12	<p>Changed “affilitates” to “affiliates”</p>	<p>Grammatical change</p>
12	<p>Added “...(i.e., de-identified).” and “The DNA samples may be shared with ancillary study investigators and possibly used for genome wide association studies (GWAS).”</p>	<p>To provide additional statement to clarify genetic sample is de-identified and may be shared with outside investigators</p>

13	Added information about the National Public Databases	To document the Steering Committee decision to obtain health status information from public databases such as USRDS, SRTR, NDI and CORR
13	Changed: <ul style="list-style-type: none"> • “obversational” to “observational” • “montoring” to “monitoring” 	Grammatical change
14	Added “Jeffrey Saland”	To document a new Steering Committee member
16, 95, 99	Changed “ jjerry@jhsph.edu ” to “jjerry@jhu.edu”	To document email change
20, 21	Changed: <ul style="list-style-type: none"> • “appromixately” to “approximately” • “Eligibility” to “Eligibility” • “Similarly” to “Similarly” 	Grammatical change
24	Changed: <ul style="list-style-type: none"> • “will identify” to “identified” • “will be” to “were” • “may include, but are” to “included, but were” • “self referral” to “self-referral” • “will be focused” to “focused” • “is” to “was” • “will” to “would” • “will place” to “placed” • “In the event that the upper limit is reached, sites will be...” to “When recruitment approached the upper limit, sites were...” • “Table 5.2.2d will be used to provide...” to “Table 5.2.2d showed...” 	To document that enrollment of cohort 2 has ended
29, 30	In the “Follow-up Schedule” section, changed months to years throughout the description and changed “up to 14 year in CKiD” to “approximately 13 years in CKiD (i.e., through V15)” and extended the description of scheduled follow-up visits to visit 14.	To simplify the language describing intervals of study visits

32	<p>Updated Table 5.4.1a and footnote (if appropriate)</p> <ul style="list-style-type: none"> • Re-arranged visit columns • Changed “Family Binder” to “Family Information” 	To document the Steering Committee decision to perform ECHO and cIMT at visits 2, 6, 10 & 14, and discontinue neurocognitive assessment at visit 9
33	<p>Updated the information describing when the cardiovascular component will be implemented. Added “(i.e., ECHO)”</p> <p>Changed “during the funding cycle from 2008 to...” to “by”</p>	To document the Steering Committee decision to perform ECHO and cIMT at visits 2, 6, 10 & 14, and provide clarification
33	Changed “In turn, the core markers...” to “The core markers...”	Grammatical change
35	<p>Changed:</p> <ul style="list-style-type: none"> • “ participate in continued follow-up” to “ participate in the continued follow-up” • “loss to follow-up or withdrawal” to “unable to reach or withdrawal (i.e., lost to regular follow-up” • “in-person, mail” to “in-person interview, mail” • “will” to “should” 	Grammatical change and the introduction of the term lost to “regular” follow-up
36, 37	<p>Added “As of the June 2014 amendment, the study discontinued collecting census block group data.”</p> <p>Deleted “Food Frequency Questionnaires will be collected at baseline and annual follow-up visits.”</p>	To document Steering Committee decision to discontinue collecting census block group data and food frequency questionnaire data
38	<p>Added:</p> <ul style="list-style-type: none"> • “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.” • “... if the assessment was not completed at the baseline visit” 	To provide clarification regarding who should complete the health literacy assessment and when the assessment should be completed
42	Changed “cystatine” to “cystatin”	Grammatical change

46	Added "... 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.	To document the Steering Committee decision to discontinue neurocognitive assessment at visit 9 and encourage follow-up testing of participants who exhibit neurocognitive deficits at visit 7
46	Deleted "for Children"	To provide the correct name of the Wechsler Memory Scale
47, 50	Changed "18 years" to "17 years" and update diagram 6.3.1.2	To document the Neurocognitive subcommittee decision to discontinue administering PedsQL-C to 18 year old participants
54	Changed "every other year" to "every four (4) years"	To document the Steering Committee decision to perform ECHO and cIMT at visits 2, 6, 10 & 14
54	Changed "can not" to "cannot"	Grammatical change
59	Changed "are" to "is"	Grammatical change
62	Updated food frequency questionnaire description	To document Steering Committee decision to discontinue food frequency questionnaire
63	Deleted "Dietary Intake" from table	To correct table
80	Deleted "either" and "or 3-day diet history"	To provide correct description
82	Changed "a" to "an"	Grammatical change

86	<p>Changed the information to describe public data tapes to:</p> <p>“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.”</p>	<p>To document the new public archive policy established by NIDDK and provide additional information regarding the KIDMAC process for de-identifying data</p>
92	<p>Added the following language to describe Alternative Methods of Consent:</p> <p>“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.</p>	<p>To document the Steering Committee decision to provide sites with other methods of consenting families</p>

	<p>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:</p> <ul style="list-style-type: none"> • 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” 	
92	Added “social security number”	To clarify that social security numbers may be part of personal information and used for the study
94	<p>Updated the Subcommittee Lists</p> <ul style="list-style-type: none"> • Changes to Kidney Disease Subcommittee <ul style="list-style-type: none"> ○ Added David Myers • Changes to Neurocognitive Subcommittee <ul style="list-style-type: none"> ○ Added Lyndsay Harshman • Changes to Cardiovascular Subcommittee <ul style="list-style-type: none"> ○ Removed Lisa Friedman ○ Replaced Thomas Kimball with Peace Madueme ○ Added Ellen Woods • Changes to Growth Subcommittee <ul style="list-style-type: none"> ○ Removed David Askenanzi ○ Added Michelle Denburg ○ Removed Lisa Friedman 	To document new members to each committee and the removal of individuals no longer participating on each subcommittee
95 – 99	Revised concept sheet submission form	To document changes to the submission form
103	Update the study timeline to reflect the milestones made since last amendment.	To document the milestones

June 2016 Amendment (Amendment 10): CKiD Protocol Amendment Table-lists the changes from 06/01/14 version of the protocol to 06/01/16

2, 8, 34	<p>Removed all references to bone biopsy. Deleted:</p> <ul style="list-style-type: none"> • “and severity of bone biopsy evidence of renal osteodystrophy” • “In order to determine the molecular/cellular mechanisms underlying adynamic bone disease and other forms of secondary renal osteodystrophy in children, in a subcohort of children, iliac crest bone biopsies will be performed and results compared with GFR, and other biomarkers such as PTH. This technique has permitted the identification of key markers of chondrocyte differentiation, including the PTH/PTHrP receptor.” • “Furthermore, data generated from a small subset of children undergoing bone biopsies at the University of California – Los Angeles plus or minus (\pm) six months prior to study entry will be incorporated in the CKiD database.” 	To document the Steering Committee decision to remove bone biopsy from the protocol
5	<p>Grammatical changes throughout the protocol Changed “will undergo” to “had”</p>	Grammatical change
6	Deleted “biannually (at even years)”	To clarify that ECHO are not performed biannually
9	Updated Figure 3.2.1	Aesthetic change
10	<p>The following site Principal Investigator (PI) was changed:</p> <ul style="list-style-type: none"> • Replaced Colin White with Tom Blydt-Hansen as PI for British Columbia Children’s Hospital • Replaced Jens Goebel with Donna Claes as PI for Cincinnati Children’s Hospital and Medical Center • Replaced Tom Blydt-Hanse with Allison Dart as PI for Children’s Hospital of Winnipeg • Replaced Bruce Morgenstern with Gina-Marie Barletta as PI for Phoenix Children’s Hospital • Replaced S. Paul Hmiel with Keefe Davis as PI for St. Louis Children’s Hospital • Added Elaine Ku as Co-PI at UCSF Children’s Hospital <p>Removed “Cardinal Glennon Hospital”</p>	<p>To document changes in the site Principal Investigator</p> <p>To document the removal of a non-participating site</p>

11	<p>The following site Principal Investigator (PI) was changed:</p> <ul style="list-style-type: none"> • Replaced Deborah Matossian with Adam Weinstein as PI for Children’s Hospital of Dartmouth • Replaced Kanwal Kher with Larry Patterson as PI for Children’s National Medical Center • Replaced Yi Cai with Alejandro Quiroga as PI for DeVos Children’s Hospital at Spectrum • Replaced Sharon Andreoli with Amy Wilson as PI for Indiana University, Riley Hospital for Children • Replaced Hiren Patel with Amy Kogon as PI for Nationwide Children’s Hospital, Ohio State University • Replaced Lynne Weiss with Joann Carlson as PI for RBHS-Robert Wood Johnson Medical School • Replaced Patrick Brophy with Jason Misurac as PI for University of Iowa • Replaced Debbie Gipson with Dave Selewski as PI for University of Michigan, Mott Hospital <p>Removed the following sites:</p> <ul style="list-style-type: none"> • “Children’s Hospital of Richmond at Virginia Commonwealth University” • “Maimonides Medical Center” • “Maria Fareri Children’s Hospital at Westchester Medical Center” • “University of North Carolina” <p>Changed “Mount Sinai Medical Center” to “Icahn School of Medicine at Mount Sinai”</p>	<p>To document changes in the site Principal Investigator</p> <p>To document the removal of a non-participating site</p> <p>To document the site’s name change</p>
12, 20-25, 30, 32, 34, 39, 64	Added information throughout regarding re-opening enrollment of cohort 3	To document the Steering Committee decision to re-open enrollment and recruit a third cohort of children with a focus on non-glomerular CKD and duration of CKD < 5 years at enrollment
12	Added “cardiac magnetic resonance imaging”	To document that Cincinnati is the central laboratory for cardiac MRI reading
13	Changed “Research Triangle Institute in Research Triangle Park, NC” to “Information Management Services (IMS)”	Minor change to document the NIDDK data repository

13	<p>Changed the information about the National Public Databases to: “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). 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.”</p>	<p>To specify which Canadian databases may be involved, the additional data to be obtained and clarify the frequency of data linking with National Public Databases.</p>
13, 14	<p>Changed the information about the Honest Broker to: “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</p>	<p>To clarify the role of the Honest Broker, specify that the Department of Biomedical and Health Informatics (DBHi) at the Children’s Hospital of Philadelphia will serve as the honest broker and delineate the process that will be used to assure the transmission of data will maintain patient confidential.</p>

	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. Upon receipt of data from the national database, the DBHi will remove the DBHi ID 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. Data will be transmitted via encrypted password-protected files.”	
16	Added “data coordinating center” and changed “two project directors” to “data coordinating center project director, Judith Jerry-Fluker”	To document that the DCC will chair the TERR subcommittee
29	Deleted “and may receive meal vouchers” and added “meals”	Minor clarification change
29	Added “(if applicable)”	Minor clarification change
29	Deleted “or pregnancy”	Minor clarification change
29	In the “Follow-up Schedule” section, added information about cohort 3.	To document the Steering Committee decision to re-open enrollment and recruit a third cohort of children with a focus on non-glomerular CKD and duration of CKD < 5 years at enrollment
32	Updated Table 5.4.1a and footnote (if appropriate) <ul style="list-style-type: none"> • Added symbol to Pre-V for Family Information • Added: <ul style="list-style-type: none"> ○ NIH Toolbox Cognition Tests ○ NIH Toolbox Emotion Tests ○ Physical Activity Monitor 	To document the Steering Committee decision to re-open enrollment and recruit a third cohort of children with non-glomerular diagnosis closer to CKD onset; and perform NIH toolbox measures and perform physical activity monitoring
35	In the “Irregular Study Visits” section, added information about cardiac MRI and deleted information about performing iohexol-based GFR.	To document the Steering Committee decision to discontinue performing iGFRs during irregular visits and clarify that cardiac MRI should be performed
35	In the “Continued Follow-up Protocol” section, deleted “the study will obtain”	Grammatical change

	Added “data will be obtained” and “Ideally,”	
38	Added “and 2015 versions of the”	To document that questions from the 2015 version of YRBS were used
38	Changed “Cohort 2” to “Cohorts 2 and 3”	To document the Steering Committee decision to re-open enrollment and recruit a third cohort of children with non-glomerular diagnosis closer to CKD onset and collect health literacy data
40	Deleted “has”	Grammatical change
41	<p>Changed the following:</p> <ul style="list-style-type: none"> • “will attempt to validate” to “validated” • “confirm” to “confirmed” • “will use” to “used” • “will also serve” to “also served” • “need” to “needed” <p>Deleted “in the study at baseline, year 1 and then every other year”</p>	Grammatical changes
41-42	<p>Added “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 1.73m²). 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 \geq 90 ml/min 1.73m² 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 1.73m². In addition, iohexol-based GFR tests will be optional for Cohort 3 participants.”</p>	To document the Steering Committee’s decision to simplify the iGFR protocol by discontinuing the measurement of iohexol GFR except for selected participants.
42	<p>Added: “<i>Processing blood collection and Make-up GFR:</i>”</p> <p>Changed sentence to “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), ...”</p>	To provide clarification

42	Changed: “We will therefore use” to “We therefore used” “will be” to “is”	Grammatical change
42	Deleted “If, after collecting GFR data during the first two years of the study for each child, the agreement between the estimated GFR based on serum creatinine measurements and the iohexol-based GFR is strong, we will consider estimating GFR in place of measuring it directly using iohexol for all future visits.”	To remove redundant/irrelevant information regarding the iGFR protocol
43	Added information describing the comparison of iGFR and 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.”	To provide documentation regarding the analysis performed to compare iGFR and eGFR
45	Changed “...the termination of study enrollment” to “...the participant no longer completing regular CKiD study visits; however, participants with positive results will be given the option to participant in the continued follow-up protocol.”	To clarify that participants with positive pregnancy test can complete the continued follow-up protocol (i.e., PIP/ePIP)
45	Added “and magnesium.”	To clarify that magnesium can be performed using surplus blood at CBL
45	Deleted “Also” and “then”	Grammatical changes
53-55	Added information about the NIH Toolbox Cognition and Emotion Batteries	To document Steering Committee’s decision to perform NIH toolbox cognition and emotion tests at selected sites
58	Added “A wireless home ambulatory blood pressure cuff may be utilized for additional measurement of blood pressures at home in some children depending on funding.”	To document an optional ancillary study
59	Changed “site’s” to “site”	Grammatical change

65	Changed “7 clinical sites” to “8 clinical sites”	Grammatical change
67	Added information that we are discontinuing the 6 minute walk test	To document Steering Committee’s decision to discontinue the 6 minute walk test
68	Added information about the Actigraph Link device to assess physical activity	To document an optional ancillary study
68	In Table: <ul style="list-style-type: none"> Deleted 6 minute walk test 	To document Steering Committee’s decision to discontinue the 6 minute walk test
69	Added “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.”	To document the Steering Committee’s decision to allow CKiD participants to participate in this optional ancillary study
86-87	The “Power Calculations for Cohort” section, Revised information about cohorts 1 and 2. Added information about the sample calculation for cohort 3.	To document the power calculation to determine sample size for cohort 3
89	Revised information about the blood certification training	To describe the new online Blood Pressure Certification procedure
89	Added “This report will summarize findings as well as suggested changes for study-wide protocols.”	To clarify the information contained in report
90	Added: “or Specific study procedure training” “or procedural training (i.e., vascular testing)”	To clarify the items covered during annual training
93	In the Summary Analytical Files section, revised information about the summary files	To clarify the summary files prepared at the data coordinating center
95	Added information about ECHO Incidental Findings	To provide information about the procedures for reporting and communicating ECHO incidental findings
96	Deleted information about “Sedation”	To provide congruency with study visit practice

97	Deleted information about 6 minute walk test	To document Steering Committee's decision to discontinue the 6 minute walk test
100	<p>Updated the Subcommittee Lists</p> <ul style="list-style-type: none"> • Changes to Kidney Disease Subcommittee <ul style="list-style-type: none"> ○ Replaced Jens Goebel with Donna Claes ○ Added Allison Dart ○ Added Alejandro Quirogo ○ Added Alice So • Changes to Neurocognitive Subcommittee <ul style="list-style-type: none"> ○ Added Amy Kogon ○ Added Joann Spinale ○ Added Cynthia Wong • Changes to Cardiovascular Subcommittee <ul style="list-style-type: none"> ○ Added Alejandro Quirogo • Changes to Growth Subcommittee <ul style="list-style-type: none"> ○ Added George Schwartz ○ Shihtien Wang 	To document new members to each committee and the removal of individuals no longer participating on each subcommittee
101 – 109	Revised concept sheet submission form	To document changes to the submission form
113	Update the study timeline to reflect the milestones made since last amendment.	To document the milestones

August 2017 Amendment (Amendment 11): CKiD Protocol Amendment Table-lists the changes from 06/01/16 version of the protocol to 08/01/17

Cover page	Changed the East Coast Clinical Coordinating Center’s address from 3535 Market Place, Philadelphia, PA 19104 to 2716 South Street, Philadelphia, PA 19146	To document the change in the East Coast Coordinating Center physical address.
Cover page,	Throughout the protocol, changed the Mid-West Clinical Coordinating Center’s name from “Children’s Mercy Hospital” to “Children’s Mercy Kansas City”	To document the Mid-West Clinical Coordinating Center’s officially changed name.
Cover page, 16, 20	Throughout the protocol, changed CKiD website address from “ www.statepi.jhsph.edu/ckid/ ” to “ https://statepi.jhsph.edu/ckid/ ”	To document the change of the website’s URL address.
10	<p>Added new sites and Principal Investigators (PI):</p> <ul style="list-style-type: none"> • Gina Marie Barletta at “Arizona Kidney Disease and Hypertension Center” • Sharon Bartosh at “University of Wisconsin” <p>Changed the following site names:</p> <ul style="list-style-type: none"> • Changed “Children’s Hospital of Boston” to “Boston Children’s Hospital” • Changed “Children’s Mercy Hospital” to “Children’s Mercy Kansas City” • Changed “Oklahoma University Health Science Center” to “University of Oklahoma Health Sciences Center” <p>The following site Principal Investigators (PI) were changed:</p> <ul style="list-style-type: none"> • Replaced Martin Turman with Anjali Nayak as PI for University of Oklahoma Health Sciences Center • Replaced Gina Marie Barletta with Martin Turman as PI for Phoenix Children’s Hospital • Removed Anthony Portale as PI for UCSF Children’s Hospital 	<p>To document new participating sites and Principal Investigators.</p> <p>To document the site’s name change.</p> <p>To document changes in the site Principal Investigator.</p>
11	<p>Added new sites and Principal Investigators (PI):</p> <ul style="list-style-type: none"> • Cheryl Sanchez-Kazi at “Loma Linda University” • Anil Mongia at “State University of New York, Downstate Medical Center” • Stefan Kiessling at “University of Kentucky” <p>Change Amy Wilson’s credentials from “PhD” to “MD”</p> <p>Removed the following site:</p> <ul style="list-style-type: none"> • “University of Florida” 	<p>To document new participating sites and Principal Investigators.</p> <p>Grammatical change.</p> <p>To document the removal of a non-participating site.</p>

12, 52	Changed Nephron website address from “https://statepiaps.jhsph.edu/nephron/groups/aspproc/” to “https://statepiaps6.jhsph.edu/nephron/groups/aspproc/”	To document the change of the website’s URL address.
12	In the “ Central Repositories ” section, added “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.” Deleted “(i.e., de-identified)”	To provide clarification that samples sent to the Repositories are coded.
13	In the “ National Public Databases ” section, added information regarding the use of external data obtained from public databases and that part of the data received will also include health information on patients not in the CKiD study (i.e. unmatched patients).	To document that data received from public databases may also include data from patients who were not CKiD participants, as well as how that data will be used analytically.
14	In the “ Honest Broker ” section, added information on the transmission of data on unmatched subjects.	To clarify that data on unmatched subjects will not contain identifiers and to specify the data transmission process to be used.
14, 15	In the “ Steering Committee ” section, made changes to members. <ul style="list-style-type: none"> • Added: <ul style="list-style-type: none"> ○ Ziya Kirkali ○ Kristin Burns ○ Rebecca Johnson ○ Derek Ng ○ Joshua Samuels ○ Sarah Smiley ○ Maleka Smith ○ Perdita Taylor-Zapata • Removed the following Steering Committee members: <ul style="list-style-type: none"> ○ Marva Moxey-Mims ○ Lynne Haverkos ○ Christopher Pierce 	To document new members and removal of individuals no longer participating on the Steering Committee.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 6: BASELINE VISIT

6.1 OVERVIEW

This section will provide a guideline for the complete set of parameters and the appropriate timelines for collection of data during the baseline period. Many of the specific details for these parameters (e.g. blood pressure measurement, sample processing and cardiovascular procedures) are discussed in more detail in their respective sections of the Manual of Procedures.

6.2 INFORMED CONSENT

6.2.1 General Principles

Federal regulations require that any person, including a child, who participates in research must do so voluntarily. Generally speaking, the investigator (or other study personnel listed on the Institutional Review Boards (IRB) or Research Ethics Board (REB) application) must ask for permission from the child's parents, and if applicable, the assent of the child to participate.

Parental Permission: Consent from the child's parents/legal guardians must be obtained before enrolling the child in a study. In addition to verbally reviewing the risks and benefits of participating in CKiD, sufficient time should be allowed for parent/legal guardians to review and ask questions prior to signing the IRB-approved informed consent document. The parent should be provided with an explanation of research procedures; a description of risks, discomforts, or inconveniences that the child might experience; and assurance that the child can withdraw from the study at any time. For the CKiD Study, one parent's permission and signature on the consent document is sufficient. Some IRBs may also require the parent/legal guardian to provide consent for their own participation in the study (parents will be asked to complete forms and questionnaires).

Child's Assent: A child whose age, maturity and psychological state make it possible for him or her to make an independent decision to participate in a study must have the chance to give assent. Assent, like consent, should be an ongoing dialogue between the investigator and the participant. It also should be documented unless the IRB waives that requirement. The investigator or other qualified study personnel should give the child: an explanation of the research procedures in language appropriate to that child; a description of any risks, discomforts, or inconveniences that the child might experience; and assurance that the child can withdraw from the study at any time.

A copy of the institutional IRB approval for the CKiD study, and a copy of the signed and dated consent form (and assent form if applicable) are mandatory prior to proceeding with the baseline procedures. This will document the agreement of the participant to participate in the study activities.

6.2.2 Participation in Other Studies

Subjects may participate in other studies if they choose to. However, they will be encouraged by CKiD study personnel not to participate in randomized clinical trials *where the treatment is unknown* during their participation in CKiD.

6.2.3 Sequence of Procedures

It is recognized that Clinical Center IRB's have official responsibility for determination of informed consent procedures. Prototype informed consent forms have been developed for the study, and each Clinical Center's IRB-approved consent form will be reviewed to make sure the essential material is included. The following description is intended as a guideline that most centers could follow.

- 1) Consent should be obtained at the time of or before the first component of the baseline visit. It will include descriptions of the interaction with members of the study team, the various measurements and procedures to be conducted throughout the study period and potential risks involved with participating in the study.
- 2) Consent for the optional donation of biological and genetic blood samples may be obtained separately or combined into a single form.
- 3) Consent for the optional use of social security number and/or name and date of birth to link CKiD study data to public health databases for future research may be obtained separately or combined into a single form.
- 4) Consent for the optional iohexol GFR test may be obtained separately or combined into a single form.

6.2.4 Privacy

At the beginning of the study, each participant is assigned an identification number. Participants are identified only by number in any individual tabulations, and it is expected that only group data will be published. If individual participant data are published, no identifying information will be included. The medical records of participants in the CKiD Study will be confidential. If required, specific study related information may be made available to the Food and Drug Administration and the National Institutes of Health. All study procedures will be consistent with requirements of HIPAA regulations.

6.3 BASELINE PROCEDURES; STEP BY STEP

The purpose of the baseline visits is to collect exposure data at the initial period of the cohort study. The types of data to be collected at baseline include measures of kidney function (GFR, blood and urine labs), cardiovascular function (blood pressure), neurocognitive function (psychologist- and self-administered questionnaires), and growth (height, weight, Tanner stage and blood labs).

6.3.1 General Data Collection: Baseline Visit 1

6.3.1.1 Targeted Physical Exam – PE Form

1. Hypertension: Standard clinical blood pressure (CBP) will be measured by a trained and certified individual at all visits using an aneroid sphygmomanometer as outlined in the cardiovascular section (see Section 16).
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 (BMI) (kg/m²). 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.

6.3.1.2 General and Medical History Information

1. Sociodemographic Information - GH Form & CBG Form
We will collect dates of birth, gender, detailed race and ethnicity of the child, parents and grandparents including parental education, occupation, and household income data. These data will be collected by parent/guardian questionnaire using standard instruments at the baseline visit. Census Block Group (CBG) was also previously collected. However, as of the June 2014 amendment, the study discontinued collecting these data.
2. Birth and Family History – GH Form
Birth weight and length, gestational age, age of developmental milestones, and complications during pregnancy and in the neonatal period will be collected by the parent/guardian questionnaire. Parents will be asked to bring a record of birth weight, length and gestational age to the baseline visit. Family health and illness information of biological parents, aunts, uncles, siblings and grandparents will be collected by a structured interview.
3. Kidney Disease History – MH Form
Detailed information on the subjects' underlying kidney disease, age at diagnosis, diagnosis workup, and other disease co-morbidity will be obtained from the parent/guardian interview and by chart review in a standardized fashion at the time of the eligibility or baseline visit.

4. Health Care Utilization – MH Form

Health care resource utilization data and insurance coverage data will be collected using questionnaires and data obtained directly from CKiD subjects via annual in-person interviews. At each follow-up visit each patient fills out a MAT form (Medical Abstraction Tracking) to track detailed information regarding hospitalizations and any procedures performed over the past year.

6.3.1.3 Physical Symptoms – Form 01

Information on kidney disease-related symptoms will be collected from structured subject and parent interviews. Participants 8 years of age and older, 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.

6.3.1.4 Assessment of Dietary Intake

Information on any herbal remedies, health supplements and/or vitamins will also be collected from structured interviews at annual visits. Food Frequency Questionnaire data was collected at the baseline and annual follow-up visits. However, as of the June 2014 amendment, the study discontinued collecting FFQ data.

6.3.1.5 Environmental Exposure

1. Medication and Supplemental Inventory – MEDS Form

Medication use (prescriptions and over-the-counter) as well as use of nutritional aids, alternative medicines and 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. 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, satisfaction, and side effects with these prescribed measures will also be assessed.

2. Smoking, Alcohol, and Drug Use – Form 02

Questionnaire will elicit information regarding environmental exposures (e.g., smoking, alcohol, drug use). Questionnaires will be administered for smoking, alcohol and illicit drug use in adolescents (≥ 12 years). This information will be captured on the Form 02 (Smoking, Alcohol, Drug Use and Physical Activity).

3. Physical Activity – Form 02

In children 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). The YRBS is a self-report instrument designed to monitor categories of priority health risk behaviors among youth. This information will be captured on the Form 02 (Smoking, Alcohol, Drug Use and Physical Activity).

4. Heavy Metal Exposure (Nail Clippings & Hair Samples)

Exposure to heavy metals (e.g., lead, mercury and cadmium) and body accumulation will be assessed through assay of blood and trace metal concentrations in hair, fingernail, and toenail clippings. At the baseline visit, nail

clippings (from fingers or toes) will be collected. Participants will be asked to trim each of their 10 fingers with a chromium-free nail clipper (to be provided) and will be asked to put the clippings in a labeled plastic bag. The nail clippings and hair sample collection form will be completed and key data entered. The bags will be stored at room temperature and then shipped to the Biosample Repository.

6.3.1.6 Health Literacy Assessment

The Short Test of Functional Health Literacy in Adults (STOFHLA), a standardized instrument, will be administered to parents/legal guardian (i.e., caregiver) of participants 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.

6.3.2 Baseline Visit 1 – GFR Visit (V1a): Kidney Function Measures

Measurement of progression of kidney disease is substantially more difficult than diagnosis 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, an additional blood sample will be collected during the study visit to maximize valid laboratory results for all subjects.

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

- GFR – Iohexol Plasma Disappearance (central laboratory, V1a measured for all Cohort 1 and 2 participants and optional for Cohort 3)
- Serum Creatinine (central laboratory, V1a)
- Estimated GFR (Updated Schwartz formula; central laboratory, V1a)
- Cystatin C (central laboratory, V1a)
- Beta-Trace Protein (central laboratory using left-over serum)
- Uric Acid (central laboratory, measured starting at V4 for cohort 1 and V1a for Cohort 2 and 3 participants)
- Proteinuria (1st morning urine protein to creatinine ratio; central laboratory, V1a)
- Urine Creatinine (1st morning urine protein to creatinine ratio; central laboratory, V1a)
- Albuminuria (1st morning urine albumin to creatinine ratio; central laboratory, V1a)

The core biochemical measures are:

- Basic Metabolic Panel includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, and glucose (central and local laboratories, V1a)
- Serum Albumin (central and local laboratories, V1a)
- Calcium (central and local laboratories, V1a)
- Phosphate (central and local laboratories, V1a)
- Complete Blood Count (local laboratory, V1a)
- Intact Parathyroid Hormone (central laboratory, V1b)
- High sensitivity C-Reactive Protein, (central laboratory, V1b)
- Glucose (pending ancillary funds fasting insulin levels will be measured)

6.3.2.1 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.

Single injection Iohexol clearance to measure GFR: If possible, two polyethylene catheters will be inserted into antecubital veins, one for injecting iohexol and one for drawing blood. A zero time blood sample is collected for serum creatinine that will be measured at the Central Laboratory by Autoanalyzer and HPLC for comparison with that measured at the local lab. Then, 5 ml of Iohexol solution (Omnipaque 300, corresponding to 647 mg Iohexol per ml) will be injected over 2 min followed by 10 ml of saline solution.

Iohexol plasma disappearance will be performed at 2 time points (120 and 300).

Using Cohort 1 and Cohort 2 iGFR measurements, investigators further examined simplifying the iohexol-based GFR component. Therefore, iohexol-based GFR tests will be optional for Cohort 3 participants.

6.3.2.2 Serum Creatinine

At all annual visits, serum will be sent centrally for measurement of creatinine.

6.3.2.3 Creatinine Based Estimates of GFR: Schwartz Formula

Originally, Schwartz 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, 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. This formula generally provides a good estimate of GFR ($r \sim 0.9$) when compared with Creatinine and inulin clearance data. However, the variation between inulin clearance and GFR estimated by Schwartz formula is about 20%-30%. 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).

The original Schwartz formula has recently 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 $0.413 * (\text{height} / \text{serum creatinine})$, provides an updated Schwartz formula to estimate GFR.

6.3.2.4 Cystatin C

Recent medical literature has suggested that Cystatin C may be a better parameter for detection of decreased GFR. We will include measurement of Cystatin C with measured GFR in the CKiD Study. Cystatin C will be measured centrally at baseline (V1a) and at all annual visits.

6.3.2.5 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 post secretory 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 for Cohort 1 and at baseline for Cohorts 2 and 3, and at all annual visits, we will measure uric acid centrally.

6.3.2.6 Proteinuria and Urine Creatinine

Proteinuria has also been documented as an independent risk factor for progressive decline in kidney function among children with CKD [Mitsnefes 2003a, Wingen 1997]. At baseline (V1a), and at all annual study visits, a first-morning urine will be assessed centrally for protein and creatinine. For children who do not wear diapers, the first morning urine will be collected at home in a container (such as a jar). Samples collected at home will be transferred into a urine collection tube at the clinical site. 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.

6.3.2.7 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.

6.3.2.8 Basic Metabolic Panel

A basic metabolic panel, consisting of serum sodium, potassium, chloride, bicarbonate, BUN, creatinine and glucose, will be assessed centrally and locally at baseline (V1a) and at all annual visits. In children, hyperglycemia and insulin resistance are associated with the metabolic syndrome, a cluster of risk factors strongly linked to CKD and CVD. As part of the metabolic panel, serum glucose will be measured centrally at baseline (V1a) and at all annual visits. Pending ancillary funding, we will measure fasting serum insulin levels to allow for an estimation of insulin resistance.

6.3.2.9 Complete Blood Count (CBC)

Anemia has been shown in adult CKD to be associated with accelerated kidney disease progression, mortality and heart disease. Thus, CBC will be measured locally every year with particular attention to the hemoglobin (mg/dl). 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.

6.3.2.10 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 (V1a) and at all annual visits.

6.3.2.11 Calcium/Phosphorous/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 (V1a), Visit 2 and every other year thereafter. Intact PTH will also be measured at the baseline visit (V1b) and every other year thereafter.

6.3.2.12 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.

6.3.2.13 Urine Pregnancy Test.

Urine pregnancy test, Human Chorionic Gonadotropin (HCG) will be assessed locally at the first and second baseline visits (V1a, V1b) 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 follow their local institutional policies and state regulations regarding how to handle positive pregnancy tests.

6.3.2.14 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.

6.3.2.15 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. The renal panel consists of a basic metabolic panel, phosphorous and albumin tests. Also, if lab results are needed immediately for clinical care, then urine will be collected for local urine protein and creatinine tests. For all tests performed centrally, the Central Biochemistry Laboratory will post results on the NEPHRON, the data management system, located at <https://statepiaps8.jhsph.edu/nephron/groups/aspproc/>. However, for clinical sites requiring immediate results, the following tests can be performed locally (in addition to the centrally performed tests):

- Proteinuria and urine creatinine
- Renal Panel
- Serum creatinine (as part of Renal Panel)
- Glucose (as part of Renal Panel)
- Albumin (as part of Renal Panel)
- Phosphate (as part of Renal Panel)

6.3.3 Baseline Visit 1 – NC Visit (V1b): Neurocognitive Measures

CKiD will conduct a battery of neurocognitive assessments at baseline (V1b). Age-specific neuropsychological tests will be administered to all study participants to measure areas of cognition, development and behavior.

The core tests for cognitive and developmental assessment are:

- Mullen Scales of Early Learning (Mullen Scales) – 6 to 29 months
 - The Mullen Scales of Early Learning is a comprehensive measure of cognitive function for children, generating 6 age-normed scores: the Gross Motor Scale, four Cognitive Scales (Visual Reception, Fine Motor, Receptive Language, and Expressive Language), and an Early Learning Composite Score.
- Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) – 30 months to 5 years
 - The WPPSI-III is a measure of general intelligence, which has been thoroughly revised to address issues of developmental sensitivity.
- Wechsler Abbreviated Scales of Intelligence Second Edition (WASI II) – 6 yrs and older
 - The WASI is designed as a reliable brief measure of general cognitive functioning, and consists of four subtests: Vocabulary, Similarities, Matrix Reasoning, and Block Design.
- Conners' Kiddie Continuous Performance Test (K-CPT) – 4 to 5 years
 - The K-CPT generates age-based standard scores for a variety of attention processes (e.g., selective attention, sustained attention, variability and reaction time).
- Conners' Continuous Performance Test II (CPT-II) – 6 and older
 - The CPT-II is used to identify visual attention problems as manifested in impaired vigilance and impulsive responding.
- 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 old
- Wechsler Intelligence Scale for Children-Integrated
 - 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

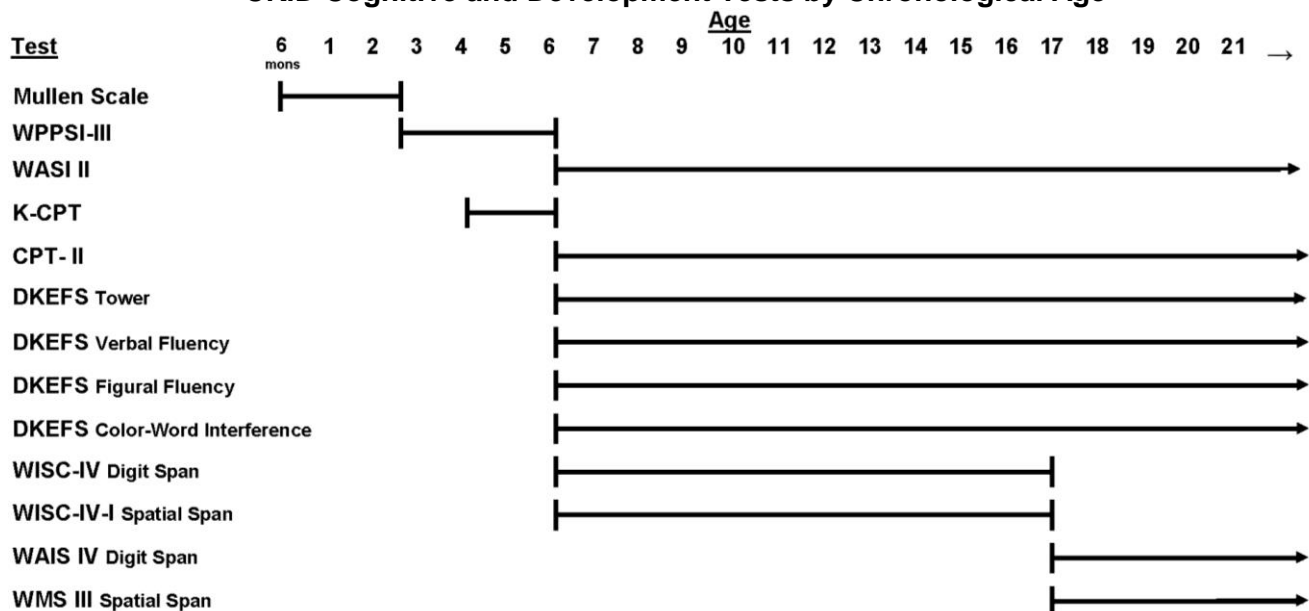
The core tests for behavioral assessment are:

- 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

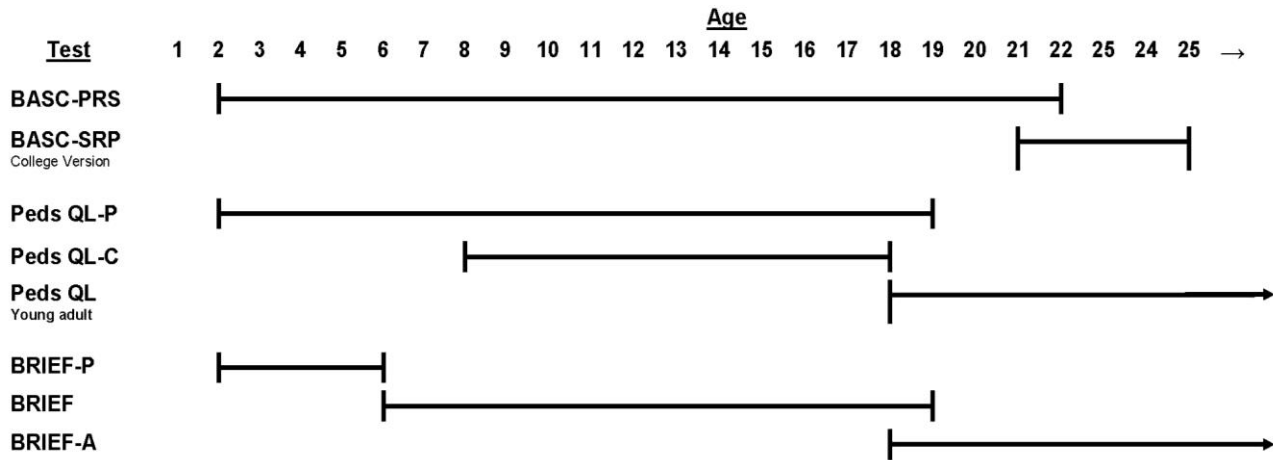
- Each version provides an evaluation of a number of scales tapping externalizing problems (e.g. hyperactivity), internalizing problems (e.g. depression), school problems (e.g., attention), adaptive skills (e.g. social skills) and other problems (e.g. withdrawal).
- Quality of Life (QOL) Scale – PedsQL for parents of children 2 years and older, children 8 to 18 years and SF-36 for children 18 years and older
 - Pediatrics QOL Scale – Parent Report (PedsQL-P) – 2 to 18 years
 - Pediatrics QOL Scale – Child Report (PedsQL-C) – 8 to 17 years
 - Pediatric QOL Scale – Young Adult (PedsQL-A) – 18 years and older
 - The PedsQL is a 23-item generic health status instrument that assesses five domains of health (Physical Functioning, Emotional Functioning, Psychosocial Functioning, Social Functioning and School Functioning)
- Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P) – 2 to 5 years old
 - The BRIEF-P is a 63-item questionnaire that assesses a child’s executive functions within the context of home and preschool environments.
- Behavior Rating Inventory of Executive Function (BRIEF) – 6 years and older
 - 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).
- Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) – 18 years and older
 - 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.

The diagrams below depict the age ranges to which each of the tests are applicable.

CKiD Cognitive and Development Tests by Chronological Age



CKiD Behavioral Assessment Tests by Chronological Age



6.3.3.1 Non-Core Neurocognitive Tests

At selected sites, new or updated versions of the following assessments will be administered:

- NIH Toolbox Cognition and Emotion Batteries
 - The NIH Toolbox is a multidimensional set of brief measures assessing cognitive, emotional, motor and sensory function from ages 3 and older. The following cognition components of the NIH Toolbox will be conducted to measure:
 - Executive Function
 - Attention
 - Episodic Memory
 - Language
 - Processing Speed
 - Working Memory

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

- Agess and Stages Questionnaire-Social Emotional (ASQ-SE-2)
 - The Age and Stages Questionnaire – Social Emotional (ASQ:SE-2) monitors very young children’s social and emotional development. It 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.
- WPPSI Fourth Edition (WPPSI-IV, an updated version of the WPPSI-III)
- BRIEF Second Edition (BRIEF2, an updated version of BRIEF parent form)
- BRIEF2 Self-Report (a new BRIEF form for participants 11 to 18 years old)

Additionally, the following assessments will continue to be administered:

- Mullen Scales of Early Learning
- WASI-II
- Parent version 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 6.3.3 will not be administered.

6.3.3.1.1 NIH Toolbox Cognition and Emotion Batteries

At selected sites, 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

The following batteries will be completed at selected sites to assess various measures of emotion.

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

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

The Age and Stages Questionnaire – Social Emotional (ASQ:SE-2) consists of a series of 9 parent completed questionnaires that screen a child from 3 months to 71 months of age.

6.3.3.1.3 Wechsler Preschool and Primary Scale of Intelligence Fourth Edition (WPPSI-IV)

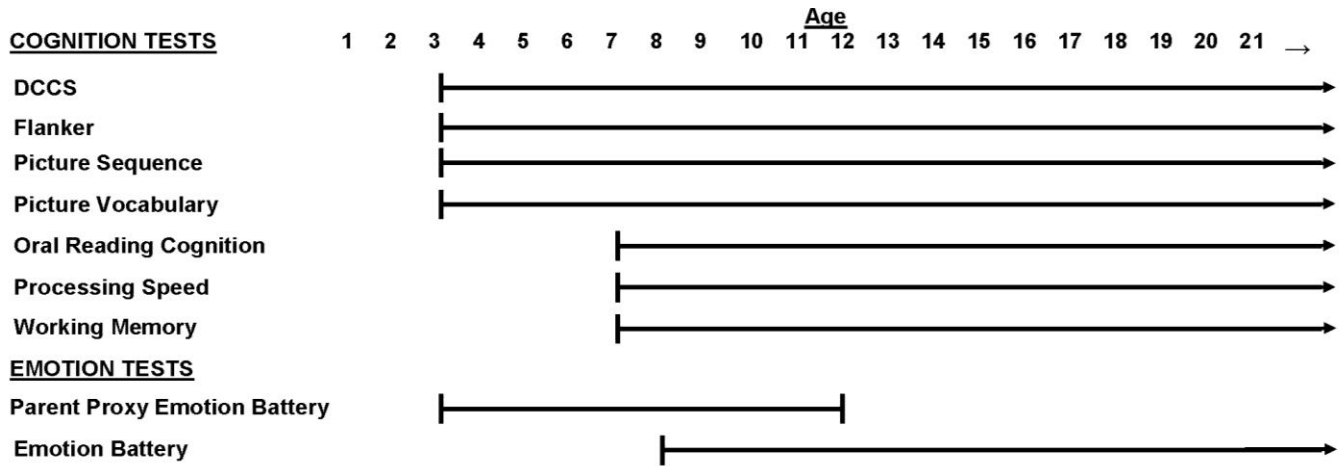
While the Wechsler Preschool and Primary Scale of Intelligence-III will continue to be used study-wide, at selected sites specific subtests of Wechsler Preschool and Primary Scale of Intelligence Fourth Edition (WPPSI-IV) will be administered. For children aged 2 years 6 months through 3 years 11 months, 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.

6.3.3.1.4 Behavior Rating of Executive Function (BRIEF)

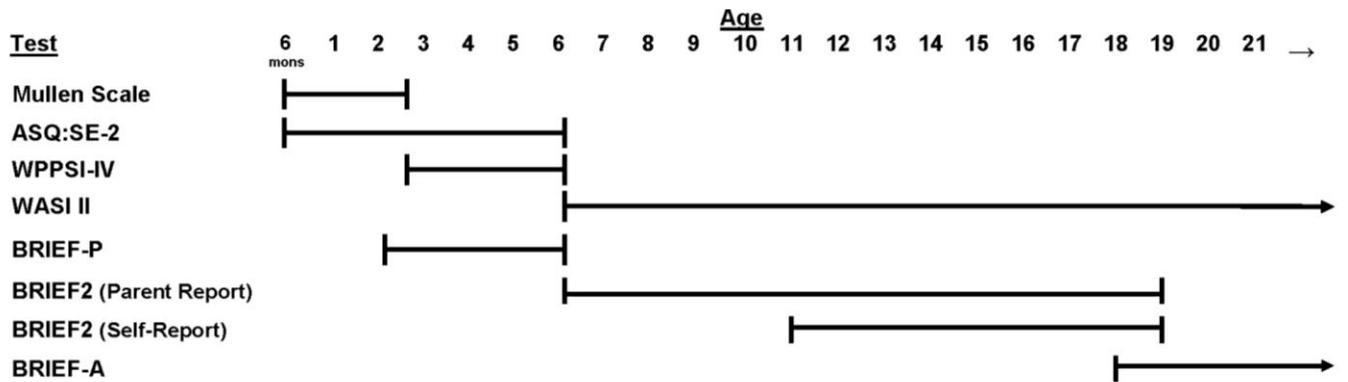
Sites will continue to administer the parent completed Behavior Rating of Executive Function Preschool version (BRIEF-P) for children ages 2 years through 5 years, and the BRIEF-Adult (BRIEF-A) for young adults 18 years old and older. However, the BRIEF parent report that is currently administered to children 6 to 18 years old will be replaced with the updated BRIEF2 parent report. 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 diagrams below depict the age ranges to which each of the tests are applicable.

NIH Toolbox Cognitive and Emotion Tests by Chronological Age for Selected Sites



CKiD Cognitive, Developmental and Behavioral Assessment Test by Chronological Age for Selected Sites



6.3.4 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. 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. At baseline and each visit thereafter, blood pressure will be measured and recorded. In addition, 24 hour ambulatory blood pressure monitoring, echocardiograms and Doppler studies, and, in a subgroup of children, carotid IMT will also be measured at all even visits (e.g., visits 2, 4, 6, 8, 10 etc.). However, as of the June 2014 Amendment, echocardiograms and Doppler studies and carotid IMT will be performed at visit 2 and then every four (4) years thereafter. These procedures will be discussed in more detail in their respective sections.

The core test to measure cardiovascular risk factors at the Baseline Visit is:

- Clinical Blood Pressure (Each visit)
- Ambulatory Blood Pressure Monitoring
- Echocardiography
- Serum Markers

6.3.4.1 Clinical Measurement of Blood Pressure – PE Form

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 Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. 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.

6.3.5 Baseline Visit (V1b): 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 2002b, Furth 2002a, Wong 2000]. Finally, there is currently limited data on the influence of poor linear growth on neurocognitive and cardiovascular outcomes.

The core tests to measure growth are:

- Height/Length (V1a and V1b)
- Body Mass Index (V1a and V1b)
- Head, Mid-Arm, Waist, Hip Circumferences (V1a and V1b)
- Intact Parathyroid Hormone (central laboratory, V1b)
- High Sensitivity C-Reactive Protein (central laboratory, V1b)
- Vitamin D (central laboratory, V1b)
- Fibroblast Growth Factor 23 (FGF-23) (central laboratory, V1b)
- Food Frequency Questionnaire (V1b) – As of the June 2014 amendment, the study discontinued collecting FFQ data

The non-core tests to measure growth are:

- Physical Activity Monitoring

6.3.5.1 Height/Length and Body Mass Index (BMI)

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. The techniques and equipment for measuring height/length will be reviewed with the principal investigator and study coordinator at each study site.

6.3.5.2 Circumferences

Circumferences will be measured as part of the physical exam at every visit. The circumferences to be measured will include head (if ≤ 3 years) and mid-arm, waist and hip circumferences for the entire cohort. Waist and hip circumference will be recorded for all visits except for children 12 months of age and/or younger who are unable to stand.

6.3.5.3 Intact Parathyroid Hormone (V1b)

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

6.3.5.4 High Sensitivity C-Reactive Protein (V1b)

Given the increasing evidence for the importance of inflammation as a marker for mortality and declining albumin in patients with CKD, inflammation may be an important variable affecting growth in children with CKD. Measurements of High Sensitivity CRP will be performed at the second baseline visit (V1b) and then every other year thereafter.

6.3.5.5 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 the second baseline visit (V1b) and then every other year thereafter.

6.3.5.6 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 the second baseline visit (V1b) and then every other year thereafter.

6.3.5.7 Food Frequency Questionnaire

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 return the completed form to the clinical site study coordinator. When the family returned the FFQ to the study coordinator, the study coordinator reviewed the forms for completeness. If missing information, the study coordinator clarified with family and sent the completed FFQs to the Clinical Coordinating Center with the other study forms. However, as of the June 2014 amendment, the study discontinued collecting FFQ data.

6.3.5.8 Non-Core Test: Physical Activity Monitoring

Physical activity will be measured using an Actigraph Link device, an FDA-approved accelerometer frequently used for research purposes. The device will collect 8 days of continuous wear data. Initially, the device will be utilized to assess physical activity in a subset of approximately 30 participants at selected clinical sites starting at visit 1b and every year thereafter. After the collection of data from 30 participants, it will be performed study-wide.

6.3.6 Other Measures: Genetic and Biological Specimens, Pregnancy Tests

Other measures include:

- Pregnancy Test (local laboratory, V1a and V1b, see Section 6.3.2.13)
- Biological Samples (repository, V1b)
- Genetic Samples (repository, V1b)

6.3.6.1 Biological Samples and Genetic Specimens (V1b)

Blood, urine, hair and nail samples will be collected at the second baseline visit (V1b). These biological specimens will be stored at the NIDDK Biosample Repository. If the sample is not collected at V1b, then the samples will be collected and shipped at the next study visit. The blood samples for storage for in the Genetic Repository will also be collected at V1b. The Genetic Repository, at Rutgers, The State University of New Jersey in Brunswick, NJ, will receive whole blood samples and process them to create immortalized cell lines and DNA samples.

6.3.7 Measurement with Time on Study as Time Scale

Topic	Variable	Year		
		0		1
		Pre-V	V1a	V1b
	Eligibility Form (Inclusion & Exclusion Criteria)	◆		
	Consent Form and Study Brochure	◆		
	Family Information	◆	◆	◆
Kidney	Iohexol-based GFR ^a		X	
	Cystatin C		X	
	Serum Creatinine		X	
	Central Renal Panel		X	
	Central Uric Acid ^b		X	
	Central Urine Creatinine and Protein		X	
	Central Urine Albumin		X	
	Local Complete Blood Count		X	
	Local Pregnancy Tests ^c		X	
	Local Renal Panel		X	
	Local Urine Creatinine and Urine Protein ^d		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 **ECCHO 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 tests.

^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 Strength:** Grip strength will be measured in participants 6 years old and older.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 7: FOLLOW-UP VISITS FOR REGULAR STUDY VISITS*

* This section refers to data measured at regular follow-up (RFU) study visits. This section does not describe the data collected at post-renal replacement therapy (post-RRT) study visits or via the continued follow-up protocol (PIP or Epip).

7.1 STUDY VISITS 2, 4, 6 and subsequent even visits

The purpose of the study visits 2, 4, 6 and subsequent even visits is to collect types of data on measures of kidney function (GFR and blood labs), cardiovascular function (blood pressure, ABPM, ECHO, carotid IMT, vascular tests and cardiac MRI), and growth (height/length, weight, head circumference, Tanner stage and physical activity). Some data such as the cardiac MRI, blood pressure and growth measures are collected at even and odd visits.

Specific information relating to all study visit procedures is provided in Section 6 “Baseline Visit”. Specific information relating to laboratory samples for each study visit is provided in Section 11 “Clinical Site Sample Collection and Handling”

A checklist form for Visit 2 and Visit 4 can be found with the packet of forms to be completed with Visit 2 and 4.

7.1.1 Visits 2, 4, ...: Data Collection

- A. Targeted Physical Exam – PE Form
- B. General and Medical History Information
 - 1. Sociodemographic Information – Form 13 & CBG
As of the **June 2014 amendment**, the study discontinued collecting CBG data
 - 2. Family History – Form 13
 - 3. Kidney Disease History – Form 14
 - 4. Health Care Utilization – Form 14
 - 5. Medical Abstraction Tracking – MAT
- C. Physical Symptoms – Form 01
- D. Food Frequency Questionnaire – As of the **June 2014 amendment**, the study discontinued collecting FFQ data
- E. Environmental Exposure
 - 1. Medication and Supplemental Inventory – MEDS Form
 - 2. Smoking, Alcohol, Drug Use and Physical Activity – Forms 12 and 17
 - 3. Heavy Metal Exposure (Fingernail Clippings and Hair Samples)
- F. Health Literacy Assessment - HLA01
Only administered if it was not completed at the baseline visit (V1A or V1B).

7.1.2 Visits 2, 4, ...: Kidney Function Measures

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

- GFR – Iohexol Plasma Disappearance (central laboratory, measured on subset of Cohorts 1 and 2 and optional for Cohort 3)
- Serum Creatinine (central laboratory)
- Estimated GFR (Schwartz formula; central laboratory)
- Cystatin C (central laboratory)
- Beta-Trace Protein (central laboratory)
- Uric Acid (central laboratory, Starting at Visit 4 for Cohort 1 and at baseline for Cohorts 2 and 3 participants)
- Proteinuria (1st morning urine protein to creatinine ratio; central laboratory)
- Urine Creatinine (1st morning urine protein to creatinine ratio; central laboratory)
- Albuminuria (1st morning urine albumin to creatinine ratio)

The core biochemical measures are:

- Basic Metabolic Panel (central and local laboratories – includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, and calcium)
- Serum Albumin (central and local laboratories)
- Calcium (central and local laboratories)
- Phosphate (central and local laboratories)
- Complete Blood Count (local laboratory)
- Glucose (pending ancillary funds fasting insulin levels will be measured)

7.1.3 Visits 2, 4, ...: Neurocognitive Measures

At all study visits, the PedsQL will be administered to parents of children 2 -18 years old, and children age 8 and older. Participants 18 years and older will complete the young adult version of the PedsQL.

7.1.4 Visits 2, 4, ...: Cardiovascular Measures

As of the June 2014 Amendment, ECHO and carotid artery intima media thickness will be performed at visit 2 and then every four years thereafter (i.e., V2, V6, V10...).

The core tests to measure cardiovascular risk factors are:

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

The non-core tests to measure cardiovascular risk factors are:

- Carotid Artery Intima Media Thickness
- Vascular Tests
- Cardiac Magnetic Resonance Imaging

7.1.4.1 Clinical Measurement of Blood Pressure – PE Form

Blood pressure will be measured in a standard fashion by trained, certified observers using an aneroid sphygmomanometer. Specific information relating to the blood pressure training and certification is provided in Section 27. Appropriately sized cuffs will be used as per the recommendations of the Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. 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.

7.1.4.2 Ambulatory Blood Pressure Monitoring (ABPM)

Ambulatory blood pressure monitoring provides multiple measurements of BP over a 24-hour period 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.

Twenty-four hour ABP will be measured using a SpaceLabs™ 90217 device. CKiD investigators at the University of Texas at Houston will serve as the ABPM coordinating center for dissemination and receipt of ABPM monitors. Initializing and downloading of monitors will be performed by the ABPM 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. Specific information relating to the Ambulatory Blood Pressure monitoring procedure is provided in Section 17 “ABPM”.

Depending on funding, a wireless home ambulatory blood pressure cuff may be utilized for additional measurements of blood pressure at home in some children.

7.1.4.3 Echocardiography

The echocardiogram (ECHO) and Doppler studies will be performed in all children at Visit 2 and every four years thereafter. ECHOs will be performed at all sites and recorded on videotape/CDs, 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 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/CDs will be stored at the clinical sites. ECHOs will be performed by a primary certified technician, or a secondary technician that has been trained by the certified technician. Standardized training and certification of a designated ECHO technician at each clinical center will be required (see Section 19 “ECHO”). The certified sonographer will provide training to any additional sonographers. However, in the event that a clinical site cannot complete the ECHO (i.e., certified primary technician or trained secondary technician is not available), 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 (see section 23).

ECHOs will be conducted in participants without sedation.

7.1.4.3.1 Cardiac structure

The following assessments will be conducted to evaluate cardiac structure in CKiD: Left Ventricular Mass (LVM) will be determined according to the American Society of Echocardiography criteria 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 ($\text{g}/\text{m}^{2.7}$) [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. 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. Normal geometry is defined as LVM index and relative wall thickness (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.

7.1.4.3.2 Cardiac function

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).

7.1.4.3.3 Vascular compliance

The following assessments will be conducted to evaluate vascular compliance. Thoracic aorta diameters will be measured and aortic strain, aortic root distensibility and aortic stiffness index will be calculated.

7.1.4.4 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.

As outlined in the kidney function assessment, urine protein and creatinine will be measured centrally yearly. Complete blood count, serum calcium and phosphorus will be measured locally and centrally in the entire CKiD cohort yearly. Albumin is a key marker of nutrition and is associated with CVD and CKD outcomes. Serum albumin will also be locally and centrally measured yearly in the entire CKiD cohort. Lipids: Triglycerides (TG), HDL, LDL, VLDL, total cholesterol (TC), TG, and high density lipoprotein cholesterol (HDL-C) will be measured on the entire cohort at V2 and every other year thereafter.

7.1.4.5 Non-Core Tests:

7.1.4.5.1 Carotid Artery Intima-Media Thickness

In a subgroup of Cohort 1 and 2 children enrolled in CKiD, regardless of age, carotid IMT will be determined by ultrasonographic measure at selected sites at Visit 2 and every four years thereafter. However, for Cohort 3, carotid IMT will only be performed on children 5 years of age and older. Some selected clinical sites are participating in the carotid IMT studies. Carotid artery IMT, stiffness, distensibility and other measures of vascular compliance will be determined.

7.1.4.5.2 Vascular Tests

To better characterize vascular function such as arterial stiffness, pulse wave analysis (PWA), pulse wave velocity (PWV) and heart variability (HRV) will be measured in a subgroup of children using the SphygmoCor System. Selected clinical sites that have the personnel and instrumentation will participate in the Vascular Tests sub-study. For Cohort 3, the tests will only be performed on children 5 years of age and older. PWA, PWV and HRV data will be collected at Visit 2 and every other year thereafter.

7.1.4.5.3 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. 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 are 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 (i.e., even or odd study visit) after a participant reaches an estimated GFR less than or equal to 30 ml/min/1.73m², or at an irregular visit prior to the initiation of RRT, whichever occurs first. The eGFR can be based on study visit or local values.

7.1.5 Visits 2, 4, ...: Growth Measures

The core tests to measure growth are:

- Height/Length & Weight
- Body Mass Index
- Circumferences (Head, arm, waist and hip)
- Tanner Stage
- Food Frequency Questionnaire – **As of the June 2014 amendment, the study discontinued collecting FFQ data.**

The non-core test to measure growth is:

- Physical Activity Monitoring

7.1.5.1 Non-Core Test: Physical Activity Monitoring

Physical activity will be measured using an Actigraph Link device, an FDA-approved accelerometer frequently used for research purposes. The device will collect 8 days of continuous wear data. Initially, the device will be utilized to assess physical activity in a subset of approximately 30 participants at selected clinical sites. After the collection of data from 30 participants, it will be performed study-wide every year at all follow-up visits.

7.1.6 Visits 2, 4, ...: Other Measures

- Pregnancy Tests
- Biological specimens (i.e., blood and urine samples) will be collected and shipped to the NIDDK Biosample Repository.

7.2 STUDY VISITS 3, 5, 7 and subsequent odd visits

The purpose of study visits 3, 5, 7, ... is to collect types of data on measures of kidney function (GFR, blood and urine tests), neurocognitive function (administered by psychologist or other trained personnel and self-administered questionnaires), and growth (height, weight, Tanner stage and blood tests).

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/trained personnel (refer to Table 7.3 at the end of this section 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.

A checklist form for Visits 3, 5, 7, ... can be found with the packet of forms to be completed with specific visit. Specific information relating to all study visit procedures is provided in Section 6 "Baseline Visit". Specific information relating to laboratory samples for each study visit is provided in Section 11 "Clinical Site Sample Collection and Handling".

7.2.1 Visits 3, 5, 7, ...: Data Collection

- Targeted Physical Exam – PE Form
At V3 and at subsequent odd visits (i.e., V5, V7...), leg length was recorded. However, as of the June 2016 amendment, the study discontinued collecting leg length measurements.
- General and Medical History Information
 1. Sociodemographic Information – Form 13a & CBG - **As of the June 2014 amendment, the study discontinued collecting CBG data**
 2. Family History – Form 13a
 3. Kidney Disease History – Form 14
 4. Health Care Utilization – Form 14
- Physical Symptoms – Form 01
- Food Frequency Questionnaire – As of the **June 2014 amendment, the study discontinued collecting FFQ data**
- Environmental Exposure
 1. Medication and Supplemental Inventory – MEDS Form
 2. Smoking, Alcohol, Drug Use and Physical Activity – Forms 12 and 17
 3. Nutrition and Steroid Use – Form F15 – As of the **June 2014 amendment, the study discontinued collecting steroid use data**

7.2.2 Visits 3, 5, 7, ...: Kidney Function Measures

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

- Serum Creatinine (central and local laboratories)
- Estimated GFR (Schwartz formula)
- Cystatin C (central laboratory)

The core biochemical measures are:

- Basic Metabolic Panel (central and local laboratories – includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, and calcium)
- Serum Albumin (central and local laboratories)
- Phosphate (central and local laboratories)
- Complete Blood Count (local laboratory)

7.2.3 Visits 3, 5, 7, ...: Neurocognitive Measures

Age-specific neuropsychological tests will be administered to all study participants to measure areas of cognition, development and behavior.

The core tests for cognitive and developmental assessment are:

- Mullen Scales of Early Learning (Mullen Scales) – 6 to 29 months
- Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) – 30 months to 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
- Wechsler Intelligence Scale for Children-Integrated
 - Spatial Span Subtest – 6 to 16 years
- 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
- 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 – Pre-School Version (BRIEF-P) – 2 to 5 years old
- Behavior Rating Inventory of Executive Function (BRIEF) – 6 to 18 years
- Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) – 18 years and older

7.2.3.1 Non-Core Tests:

At selected sites, new or updated versions of the following assessments will be administered:

- 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

- The following NIH Toolbox tests will be conducted for participants who are 7 years old and older 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

- 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

- Ages and Stages Questionnaire-Social Emotional (ASQ-SE-2)
 - The Age and Stages Questionnaire – Social Emotional (ASQ:SE-2) monitors very young children’s social and emotional development. It 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.

- WPPSI Fourth Edition (WPPSI-IV, an updated version of the WPPSI-III)
- BRIEF Second Edition (BRIEF2, an updated version of BRIEF parent form)
- BRIEF2 Self-Report (a new BRIEF form for participants 11-18 years old)

Additionally, the following assessments will continue to be administered:

- Mullen Scales of Early Learning
- WASI-II
- Parent version 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 7.2.3 will not be administered.

7.2.4 Visits 3, 5, 7, ...: Growth Measures

The core tests to measure growth are:

- Height/Length & Weight
- Body Mass Index
- Head, Mid-Arm, Waist and Hip Circumferences
- Tanner Stage
- Parathyroid Hormone (intact)
- High Sensitivity C-Reactive Protein
- Vitamin D
- Food Frequency Questionnaire – **As of the June 2014 amendment, the study discontinued collecting FFQ data**
- Fibroblast Growth factor 23 (FGF-23)
- 6 Minute Walk Test – As of the June 2016 amendment, the study discontinued collecting 6 Minute Walk data
- Grip Strength

The non-core test to measure growth is:

- Physical Activity Monitoring

7.2.4.1 6 Minute Walk Test (6MWT)

The 6 minute walk test is a useful measure of 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. The study coordinator recorded the distance walked, measured and recorded the participant's leg length and sent the data to the Clinical Coordinating Center. 6MWT was performed for participants who were 6 years old and older at V3 and every other year thereafter. However, as of the **June 2016 amendment, the study discontinued completing the 6MWT.**

7.2.4.2 Hand Grip Strength Test

The hand grip strength test is used to measure the maximal voluntary grip strength using a handgrip dynamometer. Grip strength will be measured for participants who are 6 years old and older starting at V3 and every other year thereafter.

7.2.5 Visits 3, 5, 7, ...: Other Measures

- Biological specimens (i.e., blood and urine samples) will be collected and shipped to the NIDDK Biosample Repository.

7.3 MEASUREMENT WITH TIME ON STUDY AS TIME SCALE FOR VISITS 2 through 15.

Topic	Variable	Year					
		2	3	4/ 8/12	6/ 10/14	5/7	9/11 13/15
		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		
	Cystatin C	X	X	X	X	X	X
	Serum Creatinine	X	X	X	X	X	X
	Central Renal Panel	X	X	X	X	X	X
	Central Uric Acid ^b	X	X	X	X	X	X
	Central Urine Creatinine and Protein	X	X	X	X	X	X
	Central Urine Albumin	X	X	X	X	X	X
	Local Complete Blood Count	X	X	X	X	X	X
	Local Pregnancy Tests ^c	X	X	X	X	X	X
	Local Renal Panel	X	X	X	X	X	X
	Local Urine Creatinine and Urine Protein ^d	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 tests.

^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 Strength:** Grip strength will be measured in participants 6 years old and older

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 8: ADDITIONAL VISITS

8.1 HOSPITALIZATIONS

Hospitalizations are documented on the Medical Abstraction Tracking Form (MAT). The Clinical Outcomes Subcommittee will review all hospitalizations.

8.2 IRREGULAR STUDY VISIT (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, 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 for these children is to attempt to capture the clinically relevant changes in exposures at low levels of GFR 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. 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 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 their last CKiD study visit prior to beginning the Phone/In-Person 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.

8.3 MAKE-UP GFR VISIT

In the event that blood samples cannot be obtained during the regular study visit (i.e., IV infiltration or inability to successfully draw 2 blood samples for iohexol), the participant ideally should be rescheduled for a make-up GFR within 3 months. The visit should not be repeated until 48 hours after the initial study visit if iohexol was infused. The pre-iohexol blood draw (blood collected pre-iohexol infusion for CBL chemistries, creatinine, 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, only a 1 mL Iohexol blank (B0) sample and 2 blood samples for determining the iohexol concentrations, renal panel serum and cystatin C will be collected.

Also, 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 1 mL Iohexol blank (B0) and 2 blood samples for determining the iohexol concentrations, renal panel serum and cystatin c will be collected and sent to the CBL for processing and analysis. For additional information, refer to communication memo #161 and the Make-up GFR Visits frequently asked questions below.

1. When should a make-up GFR visit be completed?

There are only two circumstances in which a Make-up GFR visit should be completed.

- If some blood samples (i.e., samples for renal panel, lipid panel) are collected BUT the iohexol blood draws are NOT collected because the study is aborted, stopped or discontinued due to iohexol infiltration or some other reason.
- All blood samples collected but the iGFR is unattainable and the family is interested in obtaining a calculated iGFR measurement.

2. What samples are collected during a make-up GFR visit?

During a make-up GFR visit, sites should obtain samples for a renal panel, cystatin C, pre iohexol B0 sample, and post iohexol infusion samples at 120 and 300 minutes.

3. If some blood samples are collected at the visit but the iohexol blood draws are NOT completed, what should be done?

The site should complete the Specimen Collection Form, ship the samples that were collected to the CBL and schedule a “Make-up GFR visit” for the participant.

4. What should be done if NO blood samples are collected during a study visit?

The site should NOT complete the Specimen Collection form. The site should schedule a “Repeated Study Visit.” During the repeated study visit, complete the Specimen Collection Form and collect all samples.

8.4 DEATHS

All deaths should be documented by completing the DSEN Form.

8.5 CONTINUED FOLLOW-UP PROTOCOL

Participants will be given the option to participate in the continued follow-up protocol after they have renal replacement therapy, become pregnant, are unable to be contacted 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 will be completed via phone, an 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. 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 (\pm 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/survey will occur annually based on the anniversary baseline (V1a) date (\pm two months).

For individuals completing the on-line survey, the following will occur:

- Sites will be provided with a list of individuals eligible to complete the on-line survey.
- Sites will send each eligible individual an email. Below is an example of the email the eligible individuals will be sent.

<< THIS IS AN EXAMPLE EMAIL TO SEND TO THE PARTICIPANT/GUARDIAN. SITES MAY ALTER THE TEXT.>>



Hello <<Site should insert the name of the participant or parent/guardian>>,

We wanted to let you know that it is time to complete your CKiD Study survey. By being a part of this study you are helping us learn more about chronic kidney disease. The questions should only take approximately 10 minutes and may be completed on-line by using the link below. Please contact us at <<Site should insert coordinator's contact information>> if you prefer to complete the survey over the phone or by speaking with us in person.

Each screen of the on-line survey has instructions and the last screen will list all of your answers. Please review all of your answers before submitting to ensure your information is correct. If you have questions or have any problems with the survey please contact <<Site should insert the name of the coordinator>> at <<Site should insert coordinator's office number and/or email>>. After you complete the survey we will give you <<Site should insert type and amount of honorarium>> to compensate you for your time.

Survey link: <<link will be sent to coordinator by your CCC>>

<<Optional: For subjects seen outside of your institution, you may need to add information about the possibility of having participant sign a medical release form to comply with your institutions policy on obtaining recent laboratory measurements and physical examination results needed to complete the Follow-up Site Questionnaire (PFU02).>>

Thank you for your contributions to the CKiD study!

- Once the individual clicks on the link provided in the email, they will be directed to the on-line survey.
 - Individuals who require consent will be directed to the consent page. Below is the website's concept page.



The Chronic Kidney Disease in Children (CKiD) Follow-Up Survey

This page provides important information about this study, and explains the risks and benefits of participating.

This research is being done to find out what factors cause Chronic Kidney Disease (CKD) to become worse in children. The National Institute of Health (NIH) is working with your center to do this research. You are being asked to do this survey because you have been a part of the CKiD study.

Parents/legal guardians, who are giving permission for a child, please note: in sections that follow "you" refers to "your child".

Taking part in this study is completely voluntary. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. There is no direct benefit to you from being in this study; however the information gained from this research may help other children with CKD in the future.

If you decide to continue to take part in the study, the following will occur:

- You will fill out a survey online which takes approximately 10 minutes to complete.
- You will complete this survey once a year until July 31st, 2018. We will contact you by phone or email when it is time for you to complete the survey.
- Your health information will be collected from your kidney doctor and medical record about dialysis treatment, transplantation, laboratory results and physical exam measurements such as blood pressure, height and weight. Tests related to kidney function (such as kidney ultrasound or ambulatory blood pressure monitoring reports) may also be reviewed by a researcher selected by the CKiD study. This may be a physician outside of your institution. Any information sent for review will not include personal identifiers such as name, medical record number, social security number, and/or date of birth.

Taking part in this study has certain risks. You may get tired or bored when completing the survey or some questions may make you feel upset or uncomfortable. Being in this study will not cost you anything. You will be compensated for each survey you are asked to complete.

To perform this study, we need to collect health information about you.

Information that is entered on the study website is sent directly to the study's data management network. No data is stored on this website. All the information that is recorded for the study is only identified by a coded number. Only the CKiD researchers at your center will be able to link this code with your information. We will do our best to keep your information private and confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

People working on this study will need to see your health information and may share it with other institutions. This includes:

- Members of the research staff at your center .
- People who review research studies to assure the quality of the data or to monitor safety.
- The study's Data Coordinating Center at the Johns Hopkins School of Public Health.
- The National Institute of Health who is sponsoring this research and its designees.
- Members of the research staff at other centers and hospitals that are part of this research.
- Institutional Review Boards (IRBs)/Research Ethics Boards (REBs) for your site and federal regulatory bodies.

Results of this study may be published or presented at meetings. Your identity will be kept private in any publication or presentation. By law, we are required to protect your health information although some people and organizations who receive your information may not be required to do so under Federal privacy laws.

There is no time limit for destroying the information collected for this study. However, you can cancel your permission to use and share your information at any time by sending a letter to the study doctor at your CKiD site. Your cancellation would not affect information already obtained about you in this study.

If you have questions, please contact your clinical site coordinator. If you do not have your clinical site coordinator's contact information, click on the link below for a complete list of all CKiD sites and the phone number of the study doctor at your CKiD site.

By clicking "I WANT TO COMPLETE THE SURVEY", you consent to take part in this study and accept that you understand the information described on this page. You are also agreeing to share and/or use your health information for this research as explained above. If you do not agree to our collecting, using and sharing your health information, you cannot participate in this study.

- Individuals who do not require consent will be navigated directly to the web-page's main page for an authenticity check. Below is the authenticity page, where respondents will be required to enter their date of birth.

- In the event that the respondent would like to contact their site to ask questions, they can click on the button “Click here if you have questions, and would like to contact your CKiD study doctor” and they will be directed to the web-page that lists the contact information for all of the clinical sites. Below is an example of the top portion of the webpage.

Site Name	Study Doctor / PI	Office Number
Aron & Robert H. Lurie Children's Hospital of Chicago	Dr. Langhinan	773-327-3930
British Columbia Children's Hospital	Dr. Tom Bygt-Hansen	604-675-2000 Ext 4849
Cardinal Glennon Hospital	Dr. Ellen Wood	616-234-3010
Carolina Medical Center	Dr. Susan Massengill	704-381-8800
Children's Hospital at Montefiore	Dr. Frederick Kaskel	718-655-1120
Children's Hospital of Alabama	Dr. Sahar Fathallah	205-638-2792
Children's Hospital of Boston	Dr. Nancy Rodig	617-355-6129
Children's Hospital of Michigan	Dr. Tej Mattoo	313-969-8628
Children's Hospital of Winnipeg	Dr. Allison Dart	204-787-4947
Children's Kidney Specialists, Idaho	Dr. Randall Jenkins	503-494-7327
Children's Mercy Hospital, Kansas City	Dr. Bradley Viteraly	816-234-3010
Children's National Medical Center	Dr. Larry Patterson	202-476-2090
Children's Hospital of Philadelphia	Dr. Susan Furth	215-590-2449
Cincinnati Children's Hospital and Medical Center	Dr. Donna Claes	513-636-5571
DeVos Children's Hospital at Spectrum	Dr. Alejandro Quiraga	616-697-2400
East Carolina University	Dr. Guillermo Hidalgo	252-744-4965
Egleston Children's Hospital, Emory University	Dr. Larry Greenbaum	404-727-5750
Hospital for Sick Children (Sick Kids)	Dr. Rulan Pawlik	416-813-7654 Ext 28042
INOVA Fairfax Hospital for Children	Dr. Patty Seo-Mayer	703-970-2600
Johns Hopkins Children's Center	Dr. Meredith Atkinson	410-955-2467
Maimonides Medical Center	Dr. Juan Kapfelerman	718-283-6165
Maria Farel Children's Hospital at Westchester	Dr. Robert Weiss	914-403-7583
Medical College of Wisconsin	Dr. Cynthia Pan	414-337-7140
Icahn School of Medicine at Mount Sinai	Dr. Jeffrey M. Sataland	212-241-6187
Nationwide Children's Hospital, Ohio State Univ.	Dr. Amy Rogien	614-722-5960
Oklahoma University Health Sciences Center	Dr. Martin Turman	405-271-4409
Oregon Health and Science University	Dr. Amira Al-Uzri	503-484-7327
Phoenix Children's Hospital	Dr. Gina-Marie Barletta	602-548-0965
Rainbow Babies and Children's Hospital	Dr. Katherine Dell	216-444-1369
Riley Hospital for Children at Indiana Univ. Health	Dr. Amy Wilson	317-274-2563
RBHS - Robert Wood Johnson Medical School	Dr. Joann Carlson	735-235-7880
Seattle Children's Hospital	Dr. Joseph Flynn	206-687-2524
St. Louis Children's Hospital	Dr. Keith Davis	314-646-6003

- All individuals will have an opportunity to decline completing the survey. Below is an example of the decline page.

DECLINED

We thank you for your time. Your response has been recorded.

EXIT

- All individuals will have an opportunity to review their responses prior to submitting their survey. Below is an example of a confirmation page.

Confirmation page

Please review **ALL** of your answers prior to clicking "SUBMIT". By clicking submit, you acknowledge that you answered the questions honestly and to the best of your ability. We will not compensate participants who knowingly provide false responses.

If you would like to change any of your responses, please check the box to the left of the question you want to change and click "UPDATE". After you click update, you will be able to change the response for the question you selected.

Transplantation:

B1. Have you ever had a kidney transplant? **Yes**

B1a. How many kidney transplants have you had? **Two**

B1b. Was your most recent kidney transplant from a living relative, a living non-relative, or from a deceased donor?

Living Donor - Related

B1c. Date of Most Recent Kidney Transplant: **07/01/2012**

B1d. When you see your doctor about your kidney transplant, how does he/she say it's doing? If you have more than one kidney transplant, please answer based on your most recent transplant. **My kidney is OK but I might need another transplant or dialysis in the near future (in 1 year or so)**

B2. **In the past year**, have you talked about kidney transplant with your nephrologist or health care provider? **Yes**

B3. Which donor option(s) has/have been discussed?

Living Donor: **Yes**

Transplant Wait List/Deceased Donor: **Yes**

B4. Have you been listed for deceased donor transplantation, in other words, are you on a transplant waiting list? **Yes**

B4a. Date activated on the waiting list: **I don't know/I'm not sure**

Dialysis:

B5. Have you ever been on dialysis? **Yes**

B5a. What type of dialysis did you use most recently: **Peritoneal Dialysis (cleansing the blood using the patient's own body tissues inside the body)**

B5b. Date Most Recent Dialysis was Started: **07/01/2011**

B5c. Are you on dialysis right now? **No**

B6. **In the past year**, have you talked about dialysis with your nephrologist or health care provider? **Yes**

B7. What type of dialysis was planned? **No Decision Yet**

99%

<< BACK **Update >>**

- For individuals who complete the survey, their respective CCC will be notified once the survey is submitted.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY
SECTION 9: GUIDELINES FOR CONDUCTING THE RESEARCH INTERVIEW

9.1 INTRODUCTION

Study Coordinators, who will be referred to as interviewers throughout this section of the Manual of Procedures, perform a variety of important functions in the CKiD study. They:

- Represent the CKiD study to the participants,
- Keep participants interested in and committed to the CKiD study,
- Provide the first line of data quality assurance,
- Detect problems participants are having and respond appropriately,
- Clarify contradictory or confusing responses, and
- Provide feedback to KIDMAC on forms.

CKiD is interested in collecting precise measurements of various aspects of the participant's demographic, medical history, and lifestyle. To obtain consistent and comparable data that give a true picture of the factual events and life experiences as well as the thoughts, actions and feelings from each participant at each site, every interviewer must collect the data using standardized interviewing techniques and procedures. To ensure that all interviewers utilize consistent interviewing methods and to minimize response bias, the CKiD researchers have carefully designed each form of the study instrument and constructed specific, detailed instructions referred to as “Question-by-Question Specifications” (QxQs) that complement each form. In addition, prior to visit 1 (the baseline visit), KIDMAC, the East Coast CCC and the Mid-West CCC held a comprehensive interviewer training session for all interviewers. Interviewers should review training material and the “Guideline to Interviewing” slide on the CKiD website : http://www.statepi.jhsph.edu/ckid/admin/ckid_admin.html.

Interviewers are extremely valuable members of the CKiD research team since the quality of the data and the success of the study depend largely upon the ability of each interviewer. They are essential to the success and future of the CKiD since they help the study to collect complete data, correct data and unbiased data.

9.2 QUESTION BY QUESTION SPECIFICATIONS (QxQs)

Question-by-Question Specifications (QxQs) serve as an intermediary between the interviewer and the CKiD researchers. They explain the purpose of questions, clarify terminology and provide additional instructions to assist the interviewer. As much pertinent information as possible is included directly on the CKiD data collection forms. However, some questions and data points require more lengthy explanations, which are detailed fully in the QxQs. The form designers also tried to foresee dilemmas that may occur during the data collection process and provide resolutions in the QxQs. In order to collect complete and standardized data, interviewers should refer to the QxQs often, especially at the beginning of data collection, to ensure that they fully understand the objective of each question.

9.3. GETTING STARTED

Before you begin the interview, make sure that you have the following materials available in the interview room:

- Binder with all necessary forms (including Medical Abstraction Tracking Checklist, etc.)
- Medication Lists (can be printed from Electronic Medical Record System)
- Copy of the QxQs
- A pad of extra paper
- Two black ball-point pens
- Calendar
- Calculator
- Water
- Kleenex
- Timer (to be used as necessary)
- Lab coat or other professional interview attire to designate a change in your role

It is important to be prepared **before** you begin the interview. The more prepared you are for the full range of interview possibilities, the more you will be able to minimize the burden to the participant. There are two other tools designed to assist the interviewer in the data collection process. They are the Medical Abstraction Tracking form (MAT).

The Medical Abstraction Tracking form is used during the interviews in conjunction with the Medical History Form. This form includes questions about specific illnesses or medical procedures that the participant may have had in the past. An affirmative response serves as a prompt to the interviewer to complete a section of the Medical Abstraction Tracking form corresponding to that particular illness or medical procedure. During the interview, the interviewer must obtain information about where and when each of the self-reported illnesses was diagnosed or medical procedure performed. The information obtained will then be used to abstract information from medical records about the illness or medical procedure for ascertainment. It is important for interviewers to probe extensively and obtain as detailed information as possible when completing the Medical Abstraction Tracking form. Incomplete information will prohibit ascertainment of the reported event from occurring.

The interviewer must be sure to obtain the proper documentation for medical release of the participant's records if the participant consents to having their medical record abstracted. The process for obtaining proper documentation is site-specific. The interviewer must follow their site's procedures in obtaining consent for medical record abstraction.

9.4 GUIDELINES FOR CONDUCTING THE IN-PERSON INTERVIEW

The interviewer will ask the participant a series of questions that are very specific and at times quite personal. Utilizing the general guidelines outlined below will help the interviewer maintain control of the interview and collect complete and correct data from the participant. All interviewers should familiarize themselves with the basics of interviewing.

1. BE PREPARED

Before undertaking the first interview, it is crucial that each interviewer be very familiar with all study protocols and procedures, study forms and QxQs, form changes implemented at each visit, skip patterns, and the entire interview process.

2. ASKING THE QUESTIONS

- a. **ALWAYS REMAIN NEUTRAL.** To prevent influencing the participant's reply, the interviewer must take every precaution to avoid showing any personal feelings or judgements. Any reactions that may imply criticism, surprise, approval or disapproval of either the questions or the participant's answers will introduce bias into the interviewing situation. Interviewers should feel comfortable with the questions and the subject material of the study. If the interviewer feels uneasy, some of those negative feelings may be transmitted to the participant, and the participant will also feel uncomfortable. All interviewers should practice asking questions that they feel may cause problems, until they can be asked in a simple, straightforward, matter-of-fact manner. Through a relaxed, professional attitude, the interviewer can ease the participant's anxieties and gain their confidence. It is especially important to remain neutral while probing for clarification of an incomplete response to a question. (See "Probing," item #5.)
- b. **ASK THE QUESTIONS IN THE EXACT ORDER IN WHICH THEY ARE PRESENTED.** The form designers ordered the questions in a logical sequence; to change that sequence might alter the intent of the question and negatively affect the research. Some questions are intentionally placed after others to avoid influencing the participant's answers since the participant may try to "give us the right answer" if they hear one question before another. To steer the participant back to the correct order of answering questions you might say:

- "That's interesting, and I'd like to hear more about it, but let's wait until we..."

- c. **ASK ALL QUESTIONS (unless instructed otherwise).** If the participant provides more information than is required for a particular question, the interviewer may feel that the participant has already answered a later question without being asked formally. **DO NOT RECORD** the response to a question that the participant indirectly provides out of sequence during the interview. If the participant becomes annoyed at the repetition (and says something such as, "I just told you that"), respond pleasantly with phrases like:

- "You may have already told me this, but let me ask the question to be sure I have the correct answer."
- "I have to make sure that I have your *full* answer to that."
- "I need to ask all of these questions in the exact order to make sure we have complete information."

Do not emphasize or define words/phrases unless the form or QxQ specifies such action. Don't answer for the participant or make assumptions about what they should or would answer. Let the participant answer each question for themselves. If a participant's response contradicts previous information that they have provided, resolve this conflict with the participant before recording the answer. (See "Resolving Inconsistent Responses," item #3 below.)

- d. **ASK EACH QUESTION EXACTLY AS IT IS WORDED.** Each participant in the study should hear *exactly* the same question. Using non-standardized changes – even one or two words – can affect the entire meaning of the question and lead to bias. Although some questions could be phrased differently or more simply, every word in the question serves a purpose and is specifically designed to achieve the research goals of the project. In order to

combine the responses of all participants and analyze the data, there must be no variations in the way questions are asked.

Occasionally, the participant will ask the interviewer to define words in a question or further explain some part of a question. In this case you should check the form and QxQs for probes that might help better explain the terminology to the participant.

- e. **DISCOURAGE CONVERSATION THAT ISN'T RELATED TO THE TOPIC.** The participant may reminisce or relate a lengthy story illustrating his/her point when asked a particular question. If the participant rambles or discusses irrelevant topics, do not hesitate to gently interrupt him/her to refocus their attention. This process is known as “gaining control of the interview,” and is an extremely important part of an interviewer's job. Acknowledge the answer with a professional tone and neutral comments such as “I see” or “O.K.” and repeat the question if they didn't respond initially. At the same time, however, take precautions to avoid offending or antagonizing the participant. Politely use comments such as:
 - “That sounds very interesting, but what I need to ask is ...”
 - “I see what you mean, but let me repeat the last question ...”

This will ensure that the interviewer maintains control of the interview situation at all times.

It is suggested that the interviewer have a pad of paper readily available during the interview. If the participant asks about something not directly related to answering the interview question being asked, the interviewer should make a note of the question on the scratch paper and explain to the participant that it can be discussed later. For example: “That’s a good question. I’m going to make a note of it right here so that we don’t forget to talk about it after we have finished the interview.”

3. RESOLVING INCONSISTENT RESPONSES

The interviewer **can and should reconcile factual inconsistencies** given by the participant **WITHIN THE CONTEXT OF THE INTERVIEW SITUATION**. For example, if the participant gives conflicting information, the interviewer **must probe** under these circumstances to correct the factual discrepancy.

EXAMPLE: **General History Form (GH Form)**

- C3. Is the child a citizen of the US?
- | | | |
|--|----|----------------|
| Yes, born in the US..... | 1 | → (Skip to C4) |
| Yes, born in Puerto Rico, Guam, the US
Virgin Islands or Northern Marianas..... | 2 | |
| Yes, born abroad to American parents..... | 3 | |
| Yes, a US citizen by naturalization..... | ④ | |
| No, not a citizen of the US..... | 5 | |
| Don't Know..... | -8 | → (Skip to C4) |

- C3 a. In what country was he or she born?
- _____ United States _____

In this example, the participant responded that they were “US citizens by naturalization” but stated they were born in the “United States.” In situations such as this, the interviewer should take care not to challenge the participant. It is best to say to the participant: “I must have misunderstood – I thought you said earlier that your/the child was a US citizen by naturalization .” In this way, the interviewer appears to be the one who has made the mistake, not the participant. In most cases the participant will be happy to straighten out the facts and correct the error. This usually requires going back and repeating the questions over again to be sure the participant understands them correctly.

NOTE: Factual discrepancies should be corrected only if they occur within the interviewing situation. This includes information obtained while you are greeting the participant or from casual conversation not related to a specific interview question, but not information you may “know” from a prior interaction with that participant (outside of this interview situation) or from their medical records. If a participant gives an answer that seems to conflict with information you “know” from outside of this interview situation, you should not attempt to reconcile the discrepancy.

4. MAINTAINING RAPPORT AND DEALING WITH SENSITIVE ISSUES

The rapport building process begins with the initial contact between the interviewer and participant. The interviewer should maintain a positive relationship with the participant throughout the interview to help put the participant at ease. By coming across with an attitude of acceptance and understanding, and by expressing an interest in the participant, the interviewer can create an atmosphere in which the participant feels able to speak freely without reservation. Specifically, the interviewer must find a delicate balance between presenting the questions in a professional, matter-of-fact manner without being abrupt, tactless or insensitive. It is best to avoid acting too serious or too jovial because extreme types of behavior may alarm or upset the participant, and will bias the interview.

If the participant appears nervous or indicates that he/she finds a particular question too personal, offensive or painful to answer, reassure him/her that he/she may speak freely and that all of his/her responses will be kept confidential. The interviewer's ability to maintain an environment in which the participant feels safe to speak is critical to the interview process. Basic approaches used in survey research involve emphasizing the confidentiality between the interviewer and participant as well as the importance of each individual's participation and contribution to this significant research. Using phrases such as, “I can understand that you might be concerned about the privacy of what you tell me, but let me reassure you that your answers are strictly confidential,” can help to put participants at ease during difficult points throughout the interview. Make sure you remain neutral regardless of the response given by the participant to delicate or embarrassing questions.

If a participant refuses to answer a question even after you've provided reassurances, indicate “DECLINED” or “REFUSED” by writing “-7” in the margin on the instrument and go on to the next question. Although missing data is always problematic, it is better to accept a refusal to one question than risk losing the entire interview.

5. PROBING

Initially, participants may not answer questions satisfactorily because in everyday social conversation, people often speak in vague terms. The interviewer uses probing techniques to stimulate discussion and to obtain more information when a participant's answer is not meaningful, is incomplete or does not adequately answer a question. Probing motivates participants to clarify or explain the reasons for their answers—probing also helps participants focus their attention on the specific aims of the question and eliminate irrelevant and unnecessary information from their responses. Furthermore, probing can encourage participants to think about their responses in general terms when questions require responses in broad categories such as “excellent,” “very good,” “fair” or “poor.”

The success of the interview depends largely upon the interviewer's ability to probe meaningfully and successfully without introducing bias or antagonizing the participant. To accomplish this goal, the interviewer must understand the objective of each question (by thoroughly reading the QxQs and study protocol), be able to recognize immediately when the participant's reply fails to satisfactorily answer the question or conflicts with information previously collected, and use unbiased, neutral probes while maintaining rapport with the participant.

a. When to Probe

Misunderstanding

Sometimes a participant will provide an irrelevant response to a question, but assume that he/she answered it sufficiently because they misunderstood the purpose or intent of the question. Usually the participant didn't hear or missed a key word or phrase in the question such as in the following example.

EXAMPLE:

Symptoms List (Form #01)

Thinking back on the *last month*, indicated the number of days in which your child has felt each of the symptoms listed below.

	Number of days in past month (Enter 0 if none.)
1. Nausea or being sick to you stomach?	___ ___

Response: “Well, she was nauseous three or four times this week.”

In this example, the participant did not hear or did not understand that the interviewer asked them “*Indicate the number of days(in the last month)* in which your child has felt each of the following symptoms listed below.” The interviewer should probe by repeating the question with emphasis or, if that doesn't help, by saying something like, “Later on I'll ask you how she feels in general. Right now I just need to know *the number of days in the last month* she felt nausea.”

Remembering Events

Several questions in the interview require the participant to recall events that took place throughout their life and the participant may not always be able to provide a precise answer. In such instances the interviewer should probe by asking the participant to try to give their “best estimate,” while at the same time reassuring him/her and being careful not to add to his/her frustration if they cannot remember exact dates. The example below from follow-up illustrates another need for probing.

EXAMPLE: Medical History Form (MH Form)

- B1. How old was your child when you or another family member became first aware of his/her kidney problem?

___ ___ years of age

Don't Know..... -8

Response: “It was right before my birthday last year.”

These types of responses require non-directive probes and the participant should be asked:

Probe: “O.K., how old was your child last year?”

Don't Know

When the participant answers, “I don't know,” it doesn't necessarily mean that the person doesn't have a response to the question. Instead it may mean that:

- i. The participant doesn't understand the question and says “*Don't Know*” to avoid admitting that they doesn't understand.
- ii. The participant needs time to think about the question and says “*Don't Know*” to break the silence and give themselves time to think more about it.
- iii. The participant may be avoiding a response because they feel uninformed, or is afraid of giving a wrong answer, or because the question seems too personal.
- iv. The participant actually may not know or may have no opinion on the question.

If a participant answers, “I don't know,” the interviewer should not be in too big of a rush to settle for that “Don't Know” response. If you sit quietly and expectantly, the participant will usually think of something to say. Reassure the participant that they can have some time to think about their answer to the question and that you are not in a hurry. Have a calendar available for the participant to use for help in determining approximate dates. Try asking in which season the event occurred, or if occurred in close proximity to a holiday or other event (e.g., relative's birthday, their husband's birthday, etc.).

If after probing, the participant can't remember the exact date of an event, but can narrow down the time period during which it could have occurred, record the date as follows:

- If the participant cannot remember the specific day, use "15" for the day.
- If the participant cannot remember the specific month, probe to determine the season and assign the month as follows:

Summer	=	July	=	07
Fall	=	October	=	10
Winter	=	January	=	01
Spring	=	April	=	04

In addition, have a calculator available to help the participant calculate totals and narrow down ranges. If the participant has trouble calculating a total (e.g., gross household income), offer to assist him/her. You can estimate a total by calculating his/her frequency of use during a known time period. For example, if he/she has had a loss of appetite three to four times per week in the past 30 days, he/she had a loss of appetite approximately 12 to 16 days (4 weeks three to four times per week). Ask him/her if this estimate sounds correct and, if so, to narrow down the range. Ask if he/she thinks they had a loss of appetite closer to 10 days or closer to 15 days in the past 30 days.

b. Correct Probing Techniques

When necessary, probes may be interspersed into the interview situation to obtain complete, accurate and clear responses without introducing bias or antagonizing the participant. The following basic principles of probing apply to all probes:

- i. The probe should in no way change the frame of reference of the question.
- ii. The probe should never indicate that one answer is expected over another.
- iii. The probe should never indicate that one answer is more socially acceptable than another.
- iv. The probe should motivate the participant to meet the question objective.
- v. The probe should never include information obtained through contact with the participant outside of the interview situation. For example, if you know the participant obtained a biopsy outside of his/her CKiD interview, but they don't remember to include it when asked on General History Form, do not include this information in a probe. Following are some of the most commonly used probing techniques:

- **Pause expectantly:**

Pausing after the participant begins to answer a question conveys that the interviewer expects them to elaborate — this is considered to be the most effective probing technique. Pausing allows the participant time to collect their thoughts.

- **Use an expression of interest and understanding:**
Saying such things as, “Uh-huh,” or “I see,” or “Yes,” communicates that the interviewer heard the response, is interested and expects the participant to say more.
- **Repeat the question:**
When the participant does not seem to understand the question, misinterprets it, seems unable to decide upon their response, or strays from the subject, repeat the question emphasizing those portions that the participant misunderstood. Many participants realize what kind of answer is needed after hearing the question a second time with emphasis.
- **Repeat the participant's reply:**
Simply repeating the participant's answer stimulates them to further thought.

- **Use neutral questions or comments:**

Neutral questions or comments such as those listed below are often used to explore many types of insufficient answers. Following are some examples of probes for various circumstances:

- **Probes To Clarify**
“What do you mean exactly?”
“What do you mean by . . .?”
“Could you please explain that a little? I don't think I quite understand.”
- **Probes For Specificity**
“What in particular do you have in mind?”
“Could you be more specific about that?”
“Tell me more about that. What/who/how/why . . .?”
- **Probes For Generality**
“Generally ... (REPEAT EXACT QUESTION).”
“Usually ...(REPEAT EXACT QUESTION).”
“What is your best estimate/guess?”
“Which choice comes closest to how you feel?”
“Which choice best matches your response?”
“There are no right or wrong answers – we're just interested in your opinion.”
- **Probes For Relevance**
“I see. Well, let me ask you again . . . (REPEAT EXACT QUESTION).”
- **Probes For Completeness**
“Anything else?”
“What else can you think of?”
“What other reasons/things/examples, etc., can you think of?”
- **Help the participant to narrow down ranges:**
For example, if, when completing the symptoms list form, the participant responds that the child was nauseated for “four to five days,” ask the participant, “Was it closer to four days or to five?” Do not just repeat the question. Explain that you can only record one answer, not a range, and ask them to state the value that most closely approximates the needed information.

c. Improper Probing Techniques

Always encourage the participant to clarify his/her responses using non-directive probing techniques without making assumptions about what he/she “really means” by their answer. Forcing the participant to choose between a reduced number of choices (as a result of an improper probe) can lead to biased data. The example below, illustrates how the interviewer makes an assumption about the participant's reply and uses an incorrect probe.

EXAMPLE:

Hypothetical question

“In general, would you say your health is”:

- Excellent..... 1
- Very Good 2
- Good 3
- Fair 4
- Poor 5

Response: “Well, you know I have kidney disease.”

Improper Probe: “Then would you say your health is fair, or poor?”

The probe in the above example forces the participant to decide between two choices, when she may feel that, despite their kidney disease, their health is excellent. We are interested in the participant's perception of their health – not a clinical assessment by a professional. The correct probing method to elicit an appropriate response to this question is to say, “Yes, but I am interested in how *you* would rate your health in general. Would you say that it is excellent, very good, good, fair or poor?”

9.5 CKiD INSTRUMENT CONVENTIONS

9.5.1 Types of Questions

The CKiD forms consist of any combination of three types of questions: pre-coded questions, open-ended questions and dependent questions.

a. Pre-coded Questions

Pre-coded questions list the response choices with an assigned numerical code for each response possibility. The simplest form of a pre-coded question requires a “yes/no” answer, while other pre-coded questions offer several possible responses. The CKiD researchers designed the response choices to be both exhaustive of every possible answer and in mutually exclusive categories. The following example is taken from the **General History Form**

EXAMPLE:

- D3. How was the child delivered?
- VAGINAL BIRTH (NATURAL)..... 1
 - CESAREAN SECTION (C-SECTION)..... 2
 - DON'T KNOW..... -8

In this case the response choices are printed in CAPITAL/UPPER CASE letters, and therefore they should not be read aloud to the participant. Use the list of responses as a guide in selecting the code that corresponds to the participant's answer. Occasionally the response choices are printed in lower case letters; lower case response choices must be read aloud to the participant.

Some data are collected in chart form as illustrated in the following example taken from the General History Form. Administration of the chart should begin by reading the introduction at the top of the page that explains what the upcoming questions are about. Next, the interviewer should read the stem question at the top of the column furthest to the left. Continue from left to right across the row until completing the question in the column to the farthest right or until being instructed to skip—which ever comes first. After completing one row, proceed to the next row, if applicable.

EXAMPLE:

INSTRUCTIONS: • **READ:** Now, I am going to ask you some more questions about the health of the child's family members.

- **COMPLETE FOR ALL FAMILY MEMBERS**
- **DOCUMENT "YES", "NO", OR "DON'T KNOW" FOR EACH**

- G6. a. Including living and deceased, have any of the **child's biological family members** been told by a health care professional (any doctor, nurse, physician assistant or nurse practitioner) that they had... b. Which **biological family members?** (Circle "Yes", "No", or "Don't Know")

1. High Blood Pressure or Hypertension		<u>Yes</u>	<u>No</u>	<u>Don't Know</u>	
Yes.....	1				
No.....	2 → (Skip to 2)				
Don't know.....	-8 → (Skip to 2)				
		Mother.....	1	2	-8
		Father.....	1	2	-8
		Sibling (full brother or sister).....	1	2	-8
		Grandparents.....	1	2	-8
		Aunts/Uncles.....	1	2	-8
		Cousins.....	1	2	-8

2. High Cholesterol		<u>Yes</u>	<u>No</u>	<u>Don't Know</u>	
Yes.....	1				
No.....	2 → (Skip to 3)				
Don't know.....	-8 → (Skip to 3)				
		Mother.....	1	2	-8
		Father.....	1	2	-8
		Sibling (full brother or sister).....	1	2	-8
		Grandparents.....	1	2	-8
		Aunts/Uncles.....	1	2	-8
		Cousins.....	1	2	-8

In the above example, after “a” there is another subquestion “b.” Be careful to ask the appropriate subquestion for each disease reported by the participant. For example, the interviewer should ask, “Which biological family members?” The interview should ask about all of the family members (mother, father etc.) **before** the interviewer proceeds to the next disease. The interviewer should carefully follow the skip patterns within each subquestion (e.g., skip to question 2 if the response to question 1 is “No,” or “Don’t Know”).

Correcting coding errors:

The majority of pre-coded questions dictate that the participant must select one answer. Based on this, the interviewer must circle one choice from the list of responses. Multiple responses are allowed only in those pre-coded questions that specifically include instructions that say “CIRCLE ALL THAT APPLY.” Circle appropriate code(s) carefully. If the interviewer hastily makes a large circle that covers two codes, the data manager cannot reconcile this problem, and the form will generate an edit report that will be sent to the interviewer for clarification. If clarification is not possible, a “missing” code will be entered into the database. If it is necessary to change a response after one choice has already been circled, draw a single line through the erroneous response, circle the correct response, and initial and date the change. Do not erase or use white out. The example below illustrates how to correct an error:

EXAMPLE:

YES.....~~1~~ HF 2/10/05
 NO.....2

OTHER, SPECIFY, DON’T KNOW and DECLINED:

Some pre-coded questions offer a choice of “OTHER” for responses that are not included or cannot be classified in one of the given categories. In addition to circling the code corresponding to “OTHER,” the question sometimes requires that the participant specify the actual answer. If required, the form will provide the instruction “SPECIFY” and space for the interviewer to record the participant’s answer verbatim.

Data collected in “SPECIFY” fields are seldom used in analyses due to the complexity of incorporating character-based data into data analysis programs. These data are mainly used in the form revision process to determine if new answer categories need to be added to a question. Therefore, if appropriate and at all possible, recode information collected via an “OTHER” response into one of the pre-coded response categories as below in this example from the General History Form.

EXAMPLE:

D15. Which of the following describe the race of the child’s biological father?
 Please respond by selecting “YES” or “NO” for each of the following. You may select yes for more than one race.

	<u>Yes</u>	<u>No</u>	<u>Don’t Know</u>
a. White.....	1	2	-8
b. Black / African American.....	1	2	-8
c. American Indian / Alaskan Native.....	1	2	-8
d. Asian.....	1	2	-8
e. Native Hawaiian / Pacific Islander.....	1	2	-8
f. Other.....	1	2	-8
1. If YES to Other, specify race:			(If No to “Other”, skip to E1)

In this example, if the participant replies that my child is other because, “My child is bi-racial because her father is African-American and I am Asian,.” this should be coded as, “Black” (code “2”) and “Asian” (code “4), not “other” and written in the the “Specify field as, “My child is bi-racial.”

“DON’T KNOW” categories have been included as answer choices for some questions. If after being probed, the participant still refuses to answer or insists that she doesn’t know and the “DON’T KNOW” category is not listed, record “-8” in the margin. If the participant REFUSES/DECLINES to answer a question, record “-7” in the margin.

Pre-coded “Mentioned/Not Mentioned” Questions:

The following is an example from General History (Question F4) that illustrates how typical pre-coded “mentioned/not mentioned” questions appear in the CKiD forms. The interviewer should ask the question, and circle “YES” for the response choices mentioned by the participant. The question specifically instructs the interviewer to circle “YES” (Code 1) for those adults who live in the primary household. All adults mentioned by the participant should be coded as “1.”

If a participant’s answer does not match any of the choices, the interviewer should circle the “YES” code for “OTHER” (Code 1) and record the response verbatim in the space provided, as indicated by “SPECIFY.”

When the participant has finished answering the question, the interviewer should ask, “any others,” and if the response is, “No,” go back and circle “NO” (Code 2) for any sources **NOT** mentioned by the participant. If the participant refuses to answer the question, do not circle any codes, but write, “-7” for DECLINED in the margin.

EXAMPLE:

F4. Which of the following adults (18 years or older) live in the primary household?

	<u>Yes</u>	<u>No</u>	<u>Don't Know</u>
a. Birth Mother	1	2	-8
b. Birth Father	1	2	-8
c. Step Mother/ Adoptive Mother	1	2	-8
d. Step Father/ Adoptive Father	1	2	-8

If the participant’s answer appears to overlap between two choices, probe for clarification and select the choice that matches the appropriate response category. The type of probe may vary depending upon the objective of the question. In the example above, the form instructs the interviewer to. This may require additional probing. The QxQs provide further instructions on how to probe to obtain the most accurate response. Record verbatim on the “SPECIFY” line responses that do not fit into the listed response categories.

b. Open-ended Questions

Open-ended questions do not contain the typical YES/NO pre-coded choices. They consist of a question followed by a space in which to record the participant’s answer. Open-ended questions require that the data collector record either the participant’s exact words or a numeric value she gives. The following example,

EXAMPLE:

C2. During the past 30 days, on how many days did you have at least one drink?

 |_|_|_|_|
 Number of DAYS

Some open-ended questions follow a pre-coded question. When an open-ended question follows a pre-coded question, it usually asks the participant to further qualify their response to the preceding pre-coded question (e.g., “How long?” “How much/many?” “When?” “Where?” “Specify”).

CKiD forms always provide space to record the answer for open-ended questions. Instructions are printed in CAPITAL letters below the answer field indicating the type of value to be recorded. The example below is taken from the General History Form; MM, DD, and YY below the lines indicate MONTH, DAY and YEAR, respectively.

EXAMPLE:

D13. What is the date of birth of the child’s biological father?

___ ___ / ___ ___ / ___ ___ ___ ___
 M M / D D / Y Y Y Y
Don’t Know..... -8

For longer, open-ended questions which require more than one piece of data—usually where the participant is asked to provide his/her thoughts, feelings, etc.—use the following guidelines:

- **Be ready to write:**
The interviewer should start writing *immediately* after the participant begins speaking in order to keep up right from the start.
- **Abbreviate:**
Use standard abbreviations. However, review the abbreviations after completion of the interview and be sure to clarify any abbreviations that may be confusing to someone else. Standard abbreviations like “DK” (don’t know), “gov’t” (government), “DECL” (declined), etc., are acceptable.
- **Ask the participant to slow down:**
People are usually flattered when they are asked to speak a little more slowly, or to repeat something, or to “wait a minute,” because the interviewer “doesn’t want to miss anything,” or wants to “get this all down.” Also, the interviewer can speak more slowly, read aloud as he/she records, or read the part of the sentence just recorded and ask the participant to complete what is not yet recorded.

When recording verbatim, the interviewer may offer encouragement by using phrases such as, “There are no right or wrong answers,” or “We’re interested in *your* opinion on this.” Remember to obtain *complete* information for each open-ended response. In the data management system, coding will be based solely on the verbatim response recorded; therefore, references to events or individuals must be clearly and fully explained. Responses such as, “Remember what I said before?” are not acceptable. It is not enough for only you, the interviewer, to understand. Since someone completely unfamiliar with the participant will be entering and trying to make sense of the data, be sure to document everything clearly. Also, no identifiers should appear on this instrument. Names of individuals are inappropriate and should be recorded as *relationships to the participant*. For example, if the participant mentions an individual by name, probe by saying “Who is (NAME)?” or “What is (NAME)’s relationship to you?”

Sometimes the participant’s initial response will be vague and unclear. Use probes that encourage the participant to CLARIFY (e.g., “What do you mean exactly?” or “What do you mean by...?”) and SPECIFY their response (e.g., “Could you be more specific about that?” or “What in particular do you have in mind?”).

c. Dependent Questions

Dependent questions can be pre-coded or open-ended and are those that are asked of only some participants. The determination of who is to be asked the question is “dependent” upon the answer to a previous question. You will be instructed in the questionnaire by what we call a “prompt” or “skip” instruction when a question is to be omitted based on a previous response. These directives to the interviewer appear in CAPITAL letters and should never be read to the participant. (For an example of a dependent question see: “Skip Instructions,” item #2b below.)

9.5.2 Instructions to the Interviewer

In addition to the questions to be asked of the participant, the questionnaire also contains instructions to the interviewer. Prompts and instructions are there to help the interviewer use the questionnaire correctly and must be followed closely. Following are some of the more common rules relating to instructions in the questionnaire.

a. Words Printed in Upper Case

The printing on the forms will appear in either UPPER CASE or lower case letters. **UPPER CASE lettering indicates that the text is instructions or guidelines for the interviewer and should NOT be read to the participant.** Material printed in lower case lettering indicates that you should read the words aloud to the participant.

b. Skip Instructions

“Skip instructions” are printed in **bold**, enclosed in parentheses or a box and located adjacent to the response code. The parenthetical skip information will either list the number of the next question the interviewer should ask, or provide a prompt within a box containing more detailed instructions.

In the following example, if the participant’s answer to question D10 is either “FULL TERM,” or “DON’T KNOW” the interviewer should skip to question D11. If the participant’s answer is “PREMATURE,” the interviewer *must* go on to the very next question, i.e., question a.

EXAMPLE:

- D10. Was the child full-term (36 weeks or more) or premature (less than 36 weeks)?
- FULL TERM 1 (Skip to D11)
PREMATURE 2
DON’T KNOW 3 (Skip to D11)

NOTE: QUESTION D10a IS ASKED **ONLY** IF THE PARTICIPANT ANSWERS “PREMATURE” TO QUESTION D10, AND IS THEREFORE A **DEPENDENT** QUESTION.

- D10a. If premature, how many weeks early was the child born?
- ___ ___ ___ weeks
- YES..... 1 (B1c)
NO..... 2

c. *Italicized* Words in Parentheses

Throughout the forms, you will find *Italicized* words or phrases in parentheses as part of certain questions. In these cases the interviewer is being instructed to insert the appropriate information while reading the question.

EXAMPLE:

- C2. Does (*name of participant*) attend school outside of the home?

In this example, the interviewer should insert participant’s name where “(name of participant)” is in the question.

d. Lower Case Words in Parentheses

Another situation you will find is when a word or phrase appears in lower case within parentheses as part of a question. In these cases, the contents of the parentheses are descriptions or synonyms of the preceding word, or further explanations of the question. Parenthetical lower case information is intended to be read aloud to the participant, at the discretion of the interviewer.

EXAMPLE:

- F5. How many children (including this child) live in the primary household?
Include **all persons under the age of 18**, including siblings and non-relatives.

- ___ ___ children
Don’t Know..... -8

e. Rounding Rules

There are some general rules regarding rounding numbered responses throughout the CKiD instrument. Specific instructions appear in the QxQs on a case-by-case basis. In general, the rule is to record the number of years to the nearest integer, rounding up to the nearest year a response of six months or more, and rounding down a response of less than six months. For example, a response of “one year and six months” would be recorded as “02 years”; whereas, “one year and three months” would be recorded as “01 year.” It is important and helpful to read question-specific instructions in the QxQs, since some questions may ask you to be more specific than others, and may have more detailed rounding rules.

9.6 ENDING THE INTERVIEW

1. MEDICAL ABSTRACTION TRACKING (MAT) FORM

As noted in Section C, upon completion of the interview, the interviewer must go back to obtain information about where and when certain illnesses were diagnosed. The information obtained will then be used to abstract information about the illness from medical records.

A participant is not required to consent to the abstraction of his/her medical record. If he/she does consent, however, the interviewer must be sure to obtain the proper documentation for medical release of the participant’s records. Remember to follow the procedures used at your site in obtaining the proper documentation for consent.

2. EDITING THE INTERVIEW

Upon completion of the interview, but before the participant leaves your site, take a few minutes to check over all completed interview forms for accuracy, completeness and legibility. If necessary, refer back to the QxQs to resolve any questions about the data collected.

- Be sure that all necessary questions were asked (unless a skip instruction expressly directed you to skip that question or series of questions). If you find that you have incorrectly skipped a question that asks for **factual information**, you should ask the participant for the information before she leaves your site. **NOTE: Questions related to attitude or feelings on the part of the participant may not be asked after the interview has been completed. If you did not ask an “attitude/feeling question” during the interview, be sure to code that question as “missing” before turning in the forms.**
- Check to be sure that the participant has provided consistent answers to factual questions. If there are inconsistent responses, you should try to resolve them while the participant is still on the premises. (See “Resolving Inconsistent Responses,” Section D.)
- Be sure to go back and fill in any missing words in your verbatim recording so that another staff person will be able to understand what you wrote.
- Go through the entire interview from the point of the data management and data entry staff. Are all of the responses coded clearly and correctly so that the data can be entered without having to generate an edit report? You can avoid edit reports by watching for those circumstances that seem questionable or unclear. If you notice a situation that may generate an edit report, record the clarifying information in the margin. By carefully reviewing your forms before turning them in, you will ultimately save yourself the time it takes to read an edit report, review the form in question, remember the reason for the problem, fill out the edit report and return the report to your data manager.

9.7 POINTS TO REMEMBER

1. FORM COPIES

A CD with a copy of each CKiD Baseline form and its QxQs is supplied by KIDMAC to the Clinical Coordinating Center at the start of each new visit. The CCC will provide a packet of forms for the participant's study visit. Site staff are responsible for making a photocopy of the completed instrument: the original copy to be sent to the CCC for data entry and the additional to be kept on file at the site. As an alternative to keeping hardcopies, site staff may store the forms in electronic format in a secure location. Use black ink to complete the forms (since colored ink does not always photocopy well).

2. ERRORS

Strike through ERRORS with a single line, and initial and date the change.

3. MARGIN NOTES

Provide notes in the margin and initial any responses that are not coded. For example:

- "Don't Know" (if it is not included as a pre-coded choice) "-8"
- "Refused" or "Declined" "-7"
- Verbatim responses that do not fall into the pre-coded choices, when the "OTHER" category is not provided

4. COMPLETING OPEN-ENDED FIELDS (LEADING ZEROS)

Enter data into every field, including ZEROS and DECIMAL PLACES for numerical data.

For example: $\frac{0}{7} \frac{4}{0} / \frac{0}{5} \frac{5}{0} \frac{5}{0}$

5. WHEN NOT TO USE ZERO

Do not use the value "0" (zero) unless it is an actual response. Zero should not be entered to represent missing (e.g., if participant doesn't know or refuses, or if interviewer missed a question) data.

EXAMPLE:

D10. What is the date of birth of the child's biological mother?

 / /
M M / D D / Y Y Y Y

Don't Know..... -8

If the the participant answers by saying something like: "She was born... in February 1965... but I really couldn't tell you the exact date," the interviewer would record "15" for the day, since the participant has told you they do not know the exact day; it would be incorrect to record 0 0, two dashes, -8, -9, or to leave the fields blank.

6. MISSING DATA AND UNLIKELY VALUES

Be sure to document if any data is missing. Ideally, of course, no data should be missing; however if the interviewer mistakenly omits a question, it should be recorded in the margin. If

there is no documentation, the interviewer will receive an edit report. Following are examples of how to record notes for missing data:

- “Interviewer error” (for omitted questions) or
- “Examiner error; not collected.”

Also, be sure to confirm unlikely, out-of-range values by entering your (interviewer/data collector’s) initials on the form in the margin next to the response. For example, if a participant says his/her child has had 75 sinus infections requiring antibiotics in the past 12 months, the interviewer would confirm this, and sign their initials indicating that she recognizes the out-of-range value but that it is, in fact, correct.

7. FINAL REVIEW

Immediately after the data is collected, before the participant leaves and while the interview is still fresh in your mind, REVIEW the forms in detail, checking for completeness and legibility. If you discover any missing, unclear or inconsistent responses, ask the participant for clarification before he/she leaves.

9.8 INTERVIEWER TRAINING

1. TRAINING NEW HIRES

a. Protocol

The trained Interviewer/Study Coordinator should begin by explaining the “big picture” to the newly hired interviewer – an overview of the CKiD and its goals, a description of the cohort, site-specific procedures, and who is available to assist them with specific problems. Review the CKiD Dossier with them to show the importance of the data they will be responsible for collecting. Emphasize that the role of the CKiD interviewer is to collect complete data, correct data, and unbiased data and that they are essential to the success and future of the study.

Review the forms, QxQs, scheduling procedures, day-to-day study procedures and resources for the participant with the new interviewer. Set up opportunities for new staff to observe more experienced staff in action. Practice with your new interviewer to ensure he/she knows skip patterns, procedures, etc.

b. Interviewing

Clearly state to the new interviewer your site’s expectations for performance and the values of your group. Let him/her sit in on real interviews, administered by more experienced staff, to get a feel for the flow of a correctly administered interview. Let him/her “score” an interview on his/her own set of forms while an interview is administered by an experienced interviewer. After the interview is done, have him/her compare their mock forms with the real forms completed by the experienced interviewer. Discuss any differences in coding and why one method is better than the other.

Encourage the new interviewer to observe how more experienced staff deal with: difficult participants, confusion about questions, interruptions, how to clarify questions without introducing bias, how to use response cards in a natural way, etc.

Observe the new interviewer administer a mock interview to a volunteer “participant” to assess their accuracy in administering the interview questions and their interpersonal skills. Once the new interviewer has begun administering real interviews to study participants,

observe one of their interviews to assess whether their skills are satisfactory and perform a performance evaluation before the end of their probationary period.

2. TRAINING FOR THE START OF STUDY (Baseline Visit) AND FUTURE VISIT WINDOWS

As soon as new forms and protocols are distributed at the beginning of each CKiD visit window, interviewers should familiarize themselves with the forms and their changes. If interviewers have questions, they should contact the Project Director at KIDMAC, Judith Jerry-Fluker at jjerry@jhu.edu. The “Changes to (FORM)” lists distributed with the forms can assist in this process. In addition, the study coordinator/interviewer should schedule a review session prior to each visit to familiarize themselves and other relevant site personnel (e.g., clinicians, phlebotomists, etc.) with visit-specific protocol issues and form changes.

3. TECHNIQUES TO IMPROVE INTERVIEW SKILLS

Study Coordinators should document specific problem areas and suggestions for improvement and share these with interviewers. Monitor progress by defining specific goals and expectations.

New interviewers should sit in on interviews conducted by experienced interviewers. Discuss these interviews and explain how and why specific questions are coded in particular ways. Discuss any difficulties and their resolutions encountered during the observed interview. In addition, experienced interviewers can role-play with new interviewers or new interviewers can observe role-playing between other staff and give constructive feedback.

4. RESOURCES AVAILABLE TO YOU

- Your CCC Project Directors and Site Principal Investigators,
- KIDMAC staff, and
- Evaluation Instrument, QxQs, interviewer training conference calls.

Interviewer trainers provide a vital service to the CKiD study; they are responsible not only for collecting complete, correct and unbiased data as interviewers themselves, but for ensuring that other site interviewers are performing satisfactorily in this role as well.

Recommended Reading:

1. Bernard, HR. *Social Research Methods: Qualitative and Quantitative Approaches*. Sage Publications, 2000.
2. Campbell, LB. *The Survey Kit*. Editor: Fink, A. Sage Publications, 1995.
3. Fowler, Jr. F and Mangione TW. *Standardized Survey Interviewing : Minimizing Interviewer-related Error*. Sage Publications, 1990.
4. Holstein JA, and Jaber F. *The Active Interview*. Sage Publications, 1995.
5. Martin RJ, Kephart DK, Dyer AM, Fahy J, and Kraft M. *Quality Control within the Asthma Clinical Research Network*. *Control Clin Trials* 2001;22:207S-221S.
6. Murphy, BC. *Interviewing in Action : Process and Practice*. Brook/Cole Publishing, 1998.
7. Picavet, HJ and Copenhagen, AN. *Health Interview Surveys: Towards International Harmonization of Methods and Instruments*. Editor deBruin,A: World Health Organization, Regional Office for Europe, 1996.
8. Schwartz N, and Sudman S. *Answering Questions : Methodology for Determining Cognitive and Communicative Processes in Survey Research*. Jossey-Bass Publishers, 1996.
9. Weisberg H, Krosnick J, and Bowen B. *An Introduction to Survey Research, Polling and Data Analysis*. Sage Publications, 1996.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 10: PHYSICAL EXAMINATION

10.1 OVERVIEW

This section describes the procedures that are to be performed during the physical examination. The CKiD physical exam is to be performed at every study visit. The physical exam consists of:

- I. Weight
- II. Length or Height
- III. Edema
- IV. Tanner Stage
- V. Temperature
- VI. Heart Rate and Blood Pressure Measurement
- VII. Urine Collection (for pregnancy testing)
- VIII. Circumferences
- IX. Leg Length - As of June 2016 amendment, 6 minute walk test was discontinued. Therefore, leg length is no longer measured

It is preferable to perform all components of the physical exam on the same day. The physical exam should be recorded on Physical Exam Form (PE Form). The PE Form has been designed to reflect the sequence in which the exams are to be performed. Following is a detailed description of what each exam component entails:

10.2 WEIGHT

MATERIALS NEEDED: An accurate scale

PROCEDURES:

An accurate scale should be used. Infants should be weighed without a diaper or any other clothing. Older children should be weighed without shoes. Please note if the participant is missing a limb. The scale should be level and on a firm surface (not a carpet). Be sure that the scale displays zero when no weight is on the scale. The older children should be instructed to stand in the middle of the scale with their head erect and eyes looking straight ahead. **The weight should be recorded in kilograms to the nearest 0.1 kg.** Instruct the child to step off the scale, reset the scale to zero, and repeat. Record each measurement. If measures differ by more than 0.2 kg., repeat a third time.

If weight is measured in pounds, the weight in pounds MUST be converted to kilograms.

1 pound = 1 pound/2.2 kilograms

Examples: **150 lbs = 150/2.2 = 68.18 = 68.2 kg**
 75 lbs = 75/2.2 = 34.09 = 34.1 kg

10.3 LENGTH/HEIGHT

Length is used for children prior to their 2nd birthday, and any child who cannot stand. Height is used for children after their 2nd birthday.

10.3.1 Measuring Length

MATERIALS NEEDED: Measuring table with a firm head block and a moveable footboard.

PROCEDURES:

Use a measuring table with a firm head block and a moveable footboard. Two people should perform the measurement. One person should hold the child's head against the head block. The child's eyes should look upward. The outer canthus of the eye and the external opening of the auditory canal should be in the same vertical plane. The second person should straighten the child's legs (or at least one leg), with the ankle at a right angle to the leg and the toes pointing upward. The second person should also bring the moveable footboard in direct contact with the sole of the foot. Two separate measurements should be taken to the nearest 0.1 cm. If the measures differ by more than 0.3 cm, then a third measurement should be taken.

10.3.2 Measuring Height

MATERIALS NEEDED: Wall-mounted stadiometer

PROCEDURES:

Use a wall-mounted stadiometer. The participant should be in bare feet. The back and buttocks should be against the wall. The heels should be together. The participant should look straight ahead, with the outer canthus of the eye and the external opening of the auditory canal in the same horizontal plane. The participant should be gently straightened upright by placing upward pressure to the mastoid process. The moveable headboard should be lowered until it gently touches the top of the head. Instruct the child to step off the stadiometer and report the height in cm. Repeat the procedure. Two separate measurements, to the nearest 0.1 cm, should be made for each child. If the measures differ by more than 0.3cm, a third measurement should be made.

10.3.3 Measuring Parental Height

MATERIALS NEEDED: Wall-mounted stadiometer

PROCEDURES:

Parental height should be obtained for at least one the child's biological parents. Use a wall-mounted stadiometer. The parent should be in bare feet. The back and buttocks should be against the wall. The heels should be together. The parent should look straight ahead, with the outer canthus of the eye and the external opening of the auditory canal in the same horizontal plane. The parent should be gently straightened upright by placing upward pressure to the mastoid process. The moveable headboard should be lowered until it gently touches the top of the head. Instruct the parent to step off the stadiometer and report the height in cm. Repeat the procedure. Two separate measurements, to the nearest 0.1 cm, should be made for the parent. If the measures differ by more than 0.3cm, a third measurement should be made.

10.4 EDEMA

If present, edema should be graded as detailed on the data collection form, where none is “0”, facial is “1,” pretibial is “2”, above knee is “3”, presacral is “4” ascites is “5”, and anasarca is “6.”

10.5 TANNER STAGE

The female Tanner stage should be determined by breast development and pubic hair and the male Tanner stage should be determined based on external genitalia and pubic hair. The person determining Tanner stage should be proficient in such assessments. The examiner may also use the laminated card and the Orchidometer (the green beads) provided in the CKiD Starter Package to assess development.

10.6 TEMPERATURE

MATERIALS NEEDED: Thermometer

PROCEDURES:

Record the participant’s temperature in Celsius (°C) or Fahrenheit (°F). Indicate on the form whether this was an oral, axillary, or Tympanic measurement.

10.7 HEART RATE AND BLOOD PRESSURE MEASUREMENT

Participants should be instructed to abstain from caffeine, smoking, and exercise at least one-half hour prior to and until completion of the blood pressure measurement as appropriate.

Part of the blood pressure measurement procedure is the measurement of the pulse, as observed by palpation of the radial artery at the wrist. For simplicity, the right arm is to be used consistently for measurement of both pulse and blood pressure. This measurement serves two purposes: (1) to document the resting heart rate at the time of examination, and (2) to permit detection of gross irregularities of heart rhythm which may affect the interpretation of the blood pressure readings.

10.7.1 Measuring Heart Rate

MATERIALS NEEDED: Accusplit (Model 80226) Stopwatch (provided in CKiD Starter Package)

PROCEDURES:

The measurement of pulse is performed only after the child has been seated quietly, with their feet flat on the floor, in an erect but comfortable posture, for at least five minutes. The child should refrain from caffeine, exercise, or strenuous activity at least one half hour prior to and until completion of heart rate measurement. The elbow and forearm should rest comfortably on the table. Measure the heart rate and record measurement as beats per minute on the Physical Examination (PE) form. Any marked irregularity observed during this period should be called to the attention of the Principal Investigator.

10.7.2 Measuring Blood Pressure

MATERIALS NEEDED: Mabis Medic-Kit Aneroid Sphygmomanometer (provided in CKiD Starter Package)

PROCEDURES:

Section 16: Blood Pressure Measurement describes the step by step procedures to be performed to obtain correct measurement of blood pressure.

10.8 URINE PREGNANCY TEST

MATERIALS NEEDED: Urine specimen container and gloves for handling specimen.

All girls who are of child-bearing potential (post menarche) should have a urine pregnancy test performed. This specimen does not need to be collected sterilely. Section 11: Clinical Site Sample Collection and Handling describes the step by step procedures to be performed to obtain urine for the pregnancy test. Positive pregnancy 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 should be done in accordance with local Institutional Review Board requirements or investigator preference. Sites should follow their local institutional policies and state regulations regarding how to handle positive pregnancy tests.

10.9 CIRCUMFERENCES

10.9.1 Measuring Head Circumference

MATERIALS NEEDED: SECA 218 (previously 402) baby band tape measure (provided in CKiD Starter Package)

PROCEDURES:

For children less than three years old, measure the greatest circumference encompassing the occipital, parietal and frontal prominences. Head circumference should be measured to the nearest millimeter. Two separate measurements should be made for each child. If the measures differ by more than 3 mm, a third measurement should be taken.

10.9.2 Measuring Mid-Arm Circumference

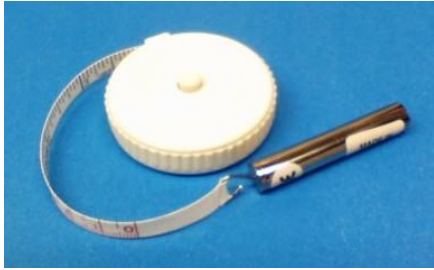
MATERIALS NEEDED: tape measure for children with large arms (provided in CKiD Starter Package)

PROCEDURES:

The participant should be standing, head looking forward, with the arms relaxed and the legs apart. Expose (bare) the child's right upper arm. If the child is missing a limb, then expose the left upper arm. Bend the elbow to 90 degrees, with the forearm palm down across the body. At the midpoint of the upper arm measure the distance between the acromion process (or bony extremity of the shoulder girdle) and the tip of the olecranon (or tip of the elbow) and mark the midpoint with a soft pen. Instruct the child to relax the arm along the side of the body, with the palm facing inwards. Measure the arm circumference by wrapping the tape measure firmly around the arm at the midpoint previously marked. Care must be taken to keep the tape measure horizontal; however avoid squeezing the arm or indenting the skin with the tape measure. Children who cannot stand, can be measured while in the supine position. A sandbag can be placed under the elbow to raise the arm slightly off the surface of the exam table or bed. Record the measure to the nearest millimeter. Two separate measurements should be made for each child. If the measures differ by more than 2 mm, a third measurement should be taken.

10.9.3 Measuring Waist Circumference

Waist circumference will be measured for the entire cohort, except for children 12 months old and/or younger who are unable to stand.



MATERIALS NEEDED: Gulick Tape Measure

The Gulick Tape Measure will be used to ensure accuracy in obtaining duplicate waist circumference measurements. The design of this tape measure eliminates the guesswork by applying a known amount of tension (four ounces) to the measuring tape. When used properly, tape tension is always four ounces. Therefore, accurate measurements are possible no matter who is doing the measuring.

This tape measure uses a no-stretch, retractable tape marked in both centimeters and inches. The tape is non-metallic, thereby eliminating the discomfort of a cold object touching the skin and any possibility of scratches or cuts. The self-retracting tape is kept at the desired length until the retract button is pushed.

The most important part of this tape measure is the tensioning device attached to the measuring tape. Its function is to provide a known amount of tension while a measurement is being taken. Each individual tensioning device is calibrated to indicate precisely a four ounce tension.

PROCEDURES:

Waist circumference should be measured for each participant under similar conditions as possible at all study visits (e.g., same time of the day, fasting, limited consumption of fluids).

Step 1: Participants should stand with their feet together. Waist Circumference will be measured in the horizontal plane 1 cm above the navel (measure 1 cm from the top of the navel with a firm ruler and mark this spot with a marker). This will usually coincide with the narrowest circumference of the trunk, but has the added advantage of being easily reproducible. The tape must be kept horizontal when making the measurements. To ensure that the tape is kept horizontal, it is best to have someone else (a parent or assistant) present when taking the measurements or to mount a full length mirror on a wall approximately 1 ½ to 2 feet from the floor. Since the circumference measurements will be made over the participant's undergarments only, a hospital gown may be worn during the measurements, but the tape should go under the gown, directly on the skin.

Step 2: The measurements must be made with the participant standing erect, abdomen relaxed, arms at the side and feet together with the participant's weight equally divided over both legs. Instruct the participant to breathe normally, to gently breathe out at the time of the measurements and to not hold in their abdomen or hold their breath (i.e., at the end of a normal expiration or air).

Step 3: *To take measurements:* Pull an appropriate amount of tape out of the housing. Wrap the tape once around the waist. Align the tape's "zero line" along side of the tape gradations. Use the metric units (cm). Then, pull on the end of the tensioning mechanism until the calibration mark is just seen. Read the measurement next to the tape's "zero line". Take one measurement, recording it to the nearest 0.1 cm and then remove the tape from the participant and take a second measurement. If the two measurements differ by 0.1 cm, then take a third measurement. Record all measurements on the Physical Examination form (PE).

Step 4: *Calibration point:* The most important part of the Gulick tape measure is its tensioning device, which provides a known amount of tension while a measurement is being taken. Each individual tensioning device is calibrated to indicate precisely a 4-ounce tension. The Gulick uses a stainless-steel compression spring – this guarantees that the calibration will last a lifetime, since it is impossible to "over-compress" a spring of this type.

10.9.4 Measuring Hip Circumference

MATERIALS NEEDED: Gulick Tape Measure

PROCEDURES:

Hip circumference will be measured for the entire cohort except for children 12 months old and/or younger who are unable to stand. The hip circumference is measured at the widest portion of the trunk and is sometimes also referred to as the buttock circumference. The child stands erect with their feet together and weight evenly distributed on both feet. While the child is holding up the examination gown (if applicable), the recorder stands in back of the child and gathers any loose fabric in the child's undergarments together above the hips and places the thumb in the fabric to make a fold. Once the recorder holds the folded undergarments snugly (if applicable), the recorder should have someone else (parent or assistant) hold the folded undergarments in place, while the recorder squats on the right side of the child so that the level of maximum extension of the buttocks can be seen and places the measuring tape around the buttocks at the maximum extension of the buttocks (see Diagram). The person assisting the recorder then adjusts the sides of the tape and checks the front and sides so that the plane of the tape is horizontal. The zero end of the tape is held under the measurement value. The tape is held snug but not tight. Take the measurement from the right side and record the measure to the nearest millimeter. Two separate measurements should be made for each child. If the measures differ by more than 1 mm, a third measurement should be taken. Record all measurements on the Physical Examination form (PE).



CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

**SECTION 11: CLINICAL SITE SAMPLE COLLECTION
AND HANDLING**

11.1 OVERVIEW OF LABORATORY RESPONSIBILITIES

- A. The clinical site CKiD coordinator will be responsible for collecting, processing and mailing all samples to the Central Biochemistry Laboratory at the University of Rochester (CBL), the clinical site's local laboratory and the appropriate repository (if applicable).
- B. The CBL will receive and perform all testing and reporting of results for the central renal panel, central urine protein, albumin and creatinine, glomerular filtration rate study based on plasma disappearance of iohexol (iohexol GFR study), intact parathyroid hormone, high sensitivity C reactive protein, lipid profile, uric acid, cystatin C, and vitamin D. Kits for these studies, and repository samples will be sent to each clinical site by the CBL.
- C. After June 2008, all cystatin C samples should be shipped to the CBL. In order to reduce shipping costs, cystatin C samples should be batched and shipped frozen with iPTH, hsCRP, vitamin D and FGF-23 samples on a quarterly basis.
- D. Participants who are enrolled in CKiD will be invited to volunteer to provide biological and genetic samples to be stored for use in ancillary studies. Serum, plasma, urine, nail clippings and hair samples will be collected and shipped to the National Institutes of Diabetes, Digestive and Kidney Disease Biosample Repository (NIDDK BR) at Fisher BioServices. Serum, plasma and urine will be collected at the second baseline visit (V1b) and at visits 2 through 15. Fisher BioServices expects to receive approximately one half of the whole blood amount obtained as plasma or serum (e.g., 2.5 mL of whole blood yields 1.25 mL of plasma or serum). Nail clippings and hair samples will be collected and shipped to NIDDK BR at the second baseline visit (V1b). At visit 4 for Cohort 1 and at V1b for Cohort 2, toenail clippings will be collected and shipped to NIDDK BR.

In addition, whole blood specimens for DNA will be collected at second baseline visit (V1b) and shipped to the National Institutes of Health Genetics Initiative at Rutgers University Cell and DNA Repository. The genetics repository requires 7.8 mL of whole blood to yield immortalized DNA. If unable to collect adequate sample at V1b, then genetic sample may be collected at a subsequent visit.

- E. The clinical site local laboratories will perform all of the testing and reporting of results for the CBC, urine pregnancy, and local renal panel.

11.2 TELEPHONE/WRITTEN COMMUNICATIONS

- A. Telephone inquiries having to do with aspects of sample collection/processing/mailing may be directed to the CBL. Calls to the CBL will be answered between 9:00 a.m. and 5:00 p.m. Eastern time, weekdays only. The phone number is (585) 275-2434 for Ms. Paula Maier (Coordinator).
- B. Written inquiries can be forwarded to the CBL via the FAX number (585) 276-2591 or e-mail CKiDCBL@urmc.rochester.edu.
- C. The CBL will communicate with participating clinical sites via electronic mail.

11.3 SUPPLIES

Supplies for the CKiD study will be provided by the CBL upon request. The study coordinators must complete the online “Iohexol/Lab Kit Request Form” located under Coordinator’s Corner on the CKiD website at <https://statepi.jhsph.edu/ckid/admin/coordinator/coordinator.html> to request generic or visit specific lab kits. Once a request for a generic lab kit is made, the generic baseline visit kit, timer, and tape measure will be sent to the site prior to the start of recruitment. As soon as a visit has been scheduled, the study coordinators must complete the online “Iohexol/Lab Kit Request Form” located under Coordinator’s Corner on the CKiD website at <https://statepi.jhsph.edu/ckid/admin/coordinator/coordinator.html> to request visit specific lab kits. Visit specific study kits will be labeled V1a and V1b for the two components that comprise the baseline visits and V2 through V15 for the subsequent visits. If additional supplies are needed at any point during this study, the study coordinator should call Paula Maier at the CBL at (585) 275-2434 or email CBL at CKIDCBL@URMC.Rochester.edu. Supplies can also be ordered on the website under Coordinator’s Corner.

The CBL will provide all the necessary shipment supplies to the clinical sites. These supplies include: cardboard outer mailing boxes, polypropylene urine transport tubes, blood collection tubes, serum and plasma transport tubes, tube labels, parafilm, zip-lock plastic bags, IATA-compliant shipping bag with absorbent gel pad, absorbent sleeves, pre-paid Fed Ex air bill, packaging instructions and, if the sample originates from an international site, a customs declaration form.

The NIDDK BR and the Rutgers DNA Repository will provide shipping supplies and collection tubes to the CBL for distribution to the clinical sites. The repository shippers contain a mailer box, absorbent material, sealing tape, FedEx air bill, packaging instruction and, if the sample originates from an international site, a customs declaration form. Serum, plasma and urine samples for NIDDK BR should be batched and shipped to the repository on a quarterly basis. Sites must complete the “NIDDK BR Shipper Request Form” on the CKiD website: <https://statepi.jhsph.edu/ckid/admin/coordinator/coordinator.html> when shippers are needed. The blood for the DNA repository should be shipped immediately after the study visit.

Visit 1a:	Visit 1b:
<ul style="list-style-type: none"> • Timer (FIRST KIT ONLY) 	<ul style="list-style-type: none"> • 1-tiger top SST for CBL blood collection and NIDDK BR sample
<ul style="list-style-type: none"> • 2-gold top SSTs for the 2-point iohexol samples with cryovial transport tubes 	<ul style="list-style-type: none"> • 2-red top cryovials for intact PTH/high sensitivity CRP (1 cryovial) and vitamin D (2nd cryovial)
<ul style="list-style-type: none"> • 1-extra gold top SST for repeat draw if necessary 	<ul style="list-style-type: none"> • 2-clear top cryovials for NIDDK BR serum samples
<ul style="list-style-type: none"> • 1-tiger top SST for pre-iohexol infusion blood draw 	<ul style="list-style-type: none"> • 2-PSTs for FGF-23 and NIDDK BR blood collection
<ul style="list-style-type: none"> • 1-2.0mL round-bottom orange top transport tube for Iohexol Blank (B0) serum 	<ul style="list-style-type: none"> • 1-green-top cryovial for FGF-23
<ul style="list-style-type: none"> • 1-4.0mL orange top transport tube for renal panel 	<ul style="list-style-type: none"> • 1-cryovial with green cap insert for NIDDK BR plasma sample
<ul style="list-style-type: none"> • 1-extra orange top transport tube for blood draw (if initial sample is grossly hemolyzed) 	<ul style="list-style-type: none"> • 1-EXTRA cryovial with green cap insert marked “PLASMA (EXTRA)” for NIDDK BR extra plasma sample
<ul style="list-style-type: none"> • 1-blue screw-top cryovial for cystatin C 	<ul style="list-style-type: none"> • 1-urine collection cup with 4 protease inhibitor tablets for NIDDK BR
<ul style="list-style-type: none"> • 1-10 mL tube for CBL urine specimen 	<ul style="list-style-type: none"> • 6-10 mL yellow top urine centrifuge tubes with removable cap
<ul style="list-style-type: none"> • 3-disposable pipettes 	<ul style="list-style-type: none"> • 7-10 mL white top cryovials for NIDDK BR urine samples
<ul style="list-style-type: none"> • Cystatin C collection and storage instructions 	<ul style="list-style-type: none"> • 3-pediatric ACD tubes for Rutgers Repository
<ul style="list-style-type: none"> • 1 blister pack and 2 absorbent sleeves for mailing specimens 	<ul style="list-style-type: none"> • 2-disposable pipettes
<ul style="list-style-type: none"> • 1 IATA-compliant specimen transport bag with absorbent gel pad 	<ul style="list-style-type: none"> • SaniZide (1 time shipment)
<ul style="list-style-type: none"> • Pre-printed Fed Ex labels and return instructions 	<ul style="list-style-type: none"> • Cryovial for nail clippings
<ul style="list-style-type: none"> • IATA-compliant shipping box for diagnostic specimens 	<ul style="list-style-type: none"> • Cryovial for toenail clippings
<ul style="list-style-type: none"> • Assembly instructions for mailing kit to CBL 	<ul style="list-style-type: none"> • zip top bag for hair sample with label
<ul style="list-style-type: none"> • Hemolysis guide 	<ul style="list-style-type: none"> • Aluminum foil for hair sample
<ul style="list-style-type: none"> • Bubble wrap 	<ul style="list-style-type: none"> • Silica gel packet for hair sample bag
<ul style="list-style-type: none"> • Snapshot 	<ul style="list-style-type: none"> • IATA-compliant shipping box for diagnostic specimens
<ul style="list-style-type: none"> • Checklist 	<ul style="list-style-type: none"> • Proper safety packaging for shipping hair & nail samples to NIDDK BR
	<ul style="list-style-type: none"> • Proper safety packaging for shipping samples to Rutgers
	<ul style="list-style-type: none"> • Assembly instructions for mailing kit to CBL
	<ul style="list-style-type: none"> • Bubble wrap
	<ul style="list-style-type: none"> • Checklist

Visits 2, 4, 6 8, 10 & 12:	Visit 3, 5, 7, 9, 11 & 13:
<ul style="list-style-type: none"> 2-gold top SSTs for the 2-point iohexol samples 2-2.0mL clear top cryovials for 2-point iohexol samples 	<ul style="list-style-type: none"> 2-tiger top SST for CBL blood collection & NIDDK BR sample 2-red top cryovials for intact PTH/high sensitivity CRP (1 cryovial) and vitamin D (2nd cryovial)
<ul style="list-style-type: none"> 1-extra gold top SST for repeat draw in case of a difficult draw 	<ul style="list-style-type: none"> 1-4.0mL orange top transport tube for renal panel and uric acid. <i>Sample for uric acid is not collected for Cohort 1</i>
<ul style="list-style-type: none"> 2-tiger top SST for CBL pre-iohexol blood draw & NIDDK BR sample 	<ul style="list-style-type: none"> 1-extra orange top transport tube for blood draw <i>(if initial sample is grossly hemolyzed)</i>
<ul style="list-style-type: none"> 1-2.0mL round-bottom orange top transport tube for Iohexol Blank (B0) serum 	<ul style="list-style-type: none"> 1- blue screw-top cryovial for cystatin C
<ul style="list-style-type: none"> 1-4.0mL orange top transport tube for renal panel and fasting lipids 	<ul style="list-style-type: none"> 2-clear top cryovials for NIDDK BR serum samples
<ul style="list-style-type: none"> 1-extra orange top transport tube <i>(if initial serum sample is grossly hemolyzed)</i> 	<ul style="list-style-type: none"> 2-PST tubes for FGF-23 and NIDDK BR blood collection
<ul style="list-style-type: none"> 1- blue screw-top cryovial for cystatin C 	<ul style="list-style-type: none"> 1-2.0mL green top cryovial for FGF-23
<ul style="list-style-type: none"> 2-clear top cryovials for NIDDK BR serum samples 	<ul style="list-style-type: none"> 1-cryovial with green cap insert for NIDDK BR plasma sample
<ul style="list-style-type: none"> 2-PSTs for NIDDK BR blood collection 	<ul style="list-style-type: none"> 2-disposable pipettes
<ul style="list-style-type: none"> 1-cryovial with green cap insert for NIDDK BR plasma sample 	<ul style="list-style-type: none"> 1-EXTRA cryovial with green cap insert marked "PLASMA (EXTRA)" for NIDDK BR extra plasma sample
<ul style="list-style-type: none"> 1-EXTRA cryovial with green cap insert marked "PLASMA (EXTRA)" for NIDDK BR extra plasma sample 	<ul style="list-style-type: none"> 1-10 mL blue top tube for CBL urine specimen
<ul style="list-style-type: none"> 4-disposable pipettes 	<ul style="list-style-type: none"> 1-urine collection cup with protease inhibitor tablets for NIDDK BR
<ul style="list-style-type: none"> 1-10 mL blue top tube for CBL urine specimen 	<ul style="list-style-type: none"> 6-10 mL yellow top urine centrifuge tubes with removable cap
<ul style="list-style-type: none"> 1-urine collection cup with 4 protease inhibitor tablets for NIDDK BR 	<ul style="list-style-type: none"> 7-10 mL white top cryovials for NIDDK BR urine samples
<ul style="list-style-type: none"> 6-10 mL yellow top urine centrifuge tubes with removable cap 	<ul style="list-style-type: none"> Cystatin C collection and storage instructions
<ul style="list-style-type: none"> 7-10 mL white top cryovials for NIDDK BR urine samples 	<ul style="list-style-type: none"> 3-absorbent sleeves
<ul style="list-style-type: none"> Cystatin C collection and storage instructions 	<ul style="list-style-type: none"> 1 IATA-compliant specimen transport bag with absorbent gel pad
<ul style="list-style-type: none"> 1 blister pack and 4 absorbent sleeves for mailing specimens 	<ul style="list-style-type: none"> Pre-printed Fed Ex labels and return instructions
<ul style="list-style-type: none"> 1 IATA-compliant specimen transport bag with absorbent gel pad 	<ul style="list-style-type: none"> IATA-compliant shipping box for diagnostic specimens
<ul style="list-style-type: none"> Pre-printed Fed Ex labels and return instructions 	<ul style="list-style-type: none"> Proper safety packaging for shipping samples to NIDDK BR
<ul style="list-style-type: none"> IATA-compliant shipping box for diagnostic specimens 	<ul style="list-style-type: none"> Assembly instructions for mailing kit to CBL
<ul style="list-style-type: none"> Assembly instructions for mailing kit to CBL 	<ul style="list-style-type: none"> 3-pediatric ACD tubes for Rutgers Repository <i>(if consent obtained and sample was either not collected or inadequate at V1b)</i> Proper safety packaging for shipping samples to Rutgers
<p>Hemolysis guide Bubble wrap Snapshot Checklist</p>	<p>IRREGULAR V3, V5, V7 V9 & VII STUDY VISIT will also include: 2-gold top SSTs for the 2-point iohexol samples 1-extra gold top SST for repeat draw if necessary 1-round-bottom orange top transport tube for B0 serum 2-2.0mL clear top cryovials for 2-point iohexol samples Hemolysis guide Bubble wrap Snapshot Checklist</p>

NOTE: For Visits 1a, 2, 4, 6, 8 and subsequent iohexol GFR study visits, one (1) 10 mL vial of iohexol will be shipped separately to the site's designated pharmacy where a syringe will be prepared and weighed for 5.0 mL of iohexol. **THE SAME SCALE MUST BE USED TO WEIGH THE SYRINGE PRE AND POST IOHEXOL INFUSION. THE SCALE MUST MEASURE TO THE 100th DECIMAL PLACE.** Detailed instructions for iohexol storage are located in Section 11.6.1.

All local sites laboratories will be responsible for providing testing supplies (i.e., tubes) to perform the local renal panel and CBC.

SHIPPING COSTS TO AND FROM THE SITES THAT ARE INCURRED IN THE STUDY WILL BE COVERED BY THE CBL, NIDDK BIOSAMPLE REPOSITORY OR RUTGERS REPOSITORY, PROVIDED THE CLINICAL SITES USE THE ENCLOSED PRE-ADDRESSED FED EX LABELS.

Samples collected for the biochemistry assays should be shipped ambient via standard overnight Fed Ex delivery to the CBL at the University of Rochester (**No Friday shipments to the CBL**). Samples collected on Friday should be refrigerated over the weekend and shipped via standard overnight Fed Ex delivery to the CBL on the next business day (i.e., Monday). The study coordinators must complete the online "Online Shipping Form" located under Coordinator's Corner on the CKiD website at <https://statepi.jhsph.edu/ckid/admin/coordinator/coordinator.html> when shipping samples. Participating clinical sites should keep a log of sample shipping dates and Fed Ex tracking numbers for reference. The CBL will log in samples received. In the event that shipping difficulties occur, the CBL will follow up as needed when notified. **The CBL will communicate sample receipt problems, any changes in handling/shipping samples, and other information to the participating clinical site's personnel and cc the corresponding Clinical Coordinating Center staff as needed.** For sites within and outside of the U.S., the CBL will use Fed Ex for shipment of participant samples. As stated, pre-printed Fed Ex labels will be included with each lab kit. Specific details on shipping repository samples are provided in 11.5.8.

Refer to section 11.5.3 for instructions on shipping cystatin C. Refer to sections 11.5.8.1 and 11.5.8.2 for instructions on shipping samples to NIDDK Biosample Repository and Rutgers DNA repository, respectively.

11.4 TYPE AND AMOUNT OF SAMPLES

Table 11.4a lists the total volume of serum and plasma that is needed for the various biochemical assays. The table includes the types of tubes and required volumes for biochemistry assays performed at the CBL. The volume indicated does not allow for rechecking any tests by the CBL.

In the event that there is a difficult blood draw for any of iohexol collections, a repeat blood draw should be performed approximately 5 minutes later (or as soon as possible) and record the exact time of the draw on the appropriate specimen collection form (L01, L21 or L41). An extra serum separator tube (SST) is provided in the lab kit for this purpose.

At V1A, the CBL has determined that 3 mL of blood in a SST, spun down, and the serum transferred to the appropriate transport tube, and maintained at room temperature is adequate for the CBL chemistries and cystatin C as well as determination of the iohexol blank. At visits 2, 4, 6, 8 and subsequent visits an additional 0.5 mL of blood will be obtained for a fasting (but not thirsting) lipid profile. This blood draw is referred to as the pre-iohexol infusion blood draw. The serum will be transferred to an orange top transport tube for shipment to the CBL. At V1b, V3, V5, V7 and subsequent odd visits, pre-infusion Iohexol level (i.e., Iohexol blank) is not needed (no Iohexol given) but 2.0 mL of blood should be collected in a SST for hsCRP, intact PTH, and vitamin D, and 1.0 mL in a PST for FGF-23 and spun down. The serum and plasma should be transferred into the appropriately labeled cryovials, stored in freezer, batched and shipped on dry ice.

For grossly hemolyzed (dark red) serum (after centrifugation): For Visits 1a, V2, V4, V6, V8 and subsequent iohexol GFR study visits, transfer appropriate amounts of serum from the tiger-top tube into the transport tube labeled “serum for CBL studies”, “cystatin C” and “B0/serum”. Perform a repeat blood draw of an additional 1.0 mL of blood for the “serum for CBL studies” at a subsequent time point. Centrifuge and transfer the serum into the **extra orange top** transport tube labeled “use for repeat serum for CBL studies”. The pre-iohexol infusion blood draw serum must be sent to the CBL regardless of the hemolysis. The fasting lipid profile is unaffected by hemolysis and will be analyzed from the initial hemolyzed sample; therefore, for pre-iohexol samples that are hemolyzed and include fasting lipid studies, the hemolyzed B0 AND “serum for CBL studies” must be sent to the CBL in addition to the repeat “serum for CBL studies”.

The 2-point iohexol samples require 1 mL of blood to be drawn in a SST at each time point of 120 and 300 minutes after iohexol infusion. If unable to draw sample at 120 and 300 minutes, draw sample as close to those time points as possible and record the actual time of the blood draw. When performing these blood draws from a saline lock, 1 mL of waste blood should be discarded before each iohexol blood draw (refer to your hospital policy if you are using extension tubing to ensure that the sample is not diluted). The samples for iohexol concentration analysis should be spun down and the serum aliquoted into separate transport tubes.

The sample requirements for the locally performed laboratory tests may vary among the clinical sites and should be determined by each clinical site. Tables 11.4a, 11.4b and 11.4c may be copied and posted in the clinical site’s blood drawing area for easy reference. Copies of the tables are provided in each kit.

11.4.1 Make-Up GFR Visit

In the event that blood samples cannot be obtained during the regular study visit (i.e., IV infiltration or an aborted study), the participant will be rescheduled for a make-up GFR within 3 months but no sooner than 48 hours after the initial study visit if iohexol was infused. The pre-infusion blood sample and first morning urine, if collected, should be sent to the CBL for processing and analysis.

If the iGFR cannot be calculated based on the iohexol results, the CBL, CCC, site and DCC, on a case by case basis, will determine whether or not a make-up GFR visit is recommended. During the make-up GFR visit, only serum for CBL studies, cystatin C, urine, B0 blank and 2 serum samples for determination of iohexol concentrations will be collected and sent to the CBL for processing and analysis.

The make-up GFR kit may be requested by completing the online “Iohexol/Lab Kit Request Form” and specifying that the visit as a make-up GFR study in the comments section and by notifying the CBL directly if the visit is scheduled within one week. The make-up GFR lab kit will include only the appropriate number of SSTs needed to conduct the 2-pt GFR study.

A urine pregnancy test should be done at local lab prior to iohexol infusion.

Table 11.4a BLOOD SAMPLES

Types of Samples	Volumes of Samples	Shipping Requirements	Ship to	Samples Collected at Study Visits			
				V1a	V1b	V2 / V4 / V6 / V8 / V10 / V12 / V14	V3 / V5 / V7 / V9 / V11 / V13 / V15
Serum for CBL chemistries^a and iohexol blank (B0)	(1) 2 or 1 mL whole blood in tiger top SST ^b , transfer 0.5mL of serum for B0 into round-bottom orange top transport tube and 0.5mL of serum for CBL chemistries into orange top transport tubes	0.5 mL of serum for B0 (V1a, V2, V4, V6, V8, V10, V12 & V14) and 0.5mL of serum for CBL chemistries at room temp (Send serum in both cryovials even if HEMOLYZED)	CBL	2		2	1
Additional Serum^d to compensate for hemolyzed chemistry sample	(1) 1.0 mL whole blood in tiger top SST ^b , transfer serum to additional orange top transport tube	0.5 mL serum, room temperature (Send with HEMOLYZED B0 serum)	CBL	1.0^d		1.0^d	1.0^d
Serum for CBL fasting lipid profile	(1) 0.5 mL whole blood in tiger top SST ^b , transfer serum to CBL chemistries orange top transport tube	0.25 mL serum, room temperature	CBL			0.5	
Blood for CBL iohexol determination	(2) 1.0 mL whole blood in SST, drawn 120 & 300mins after infusion, transfer serum to cryovial <i>(total amount of sample includes PRN waste 1 mL per blood draw)</i>	(2) 0.5 mL serum, room temperature	CBL	4		4	
Serum for Cystatin C	1 mL whole blood in tiger top SST ^b , transfer serum to blue screw-top cryovial	0.5 mL serum, frozen, shipped on dry ice (batched)	CBL	1		1	1
Blood for local CBC	Follow instructions for local lab	Send to designated local lab	Local Lab	1		1	1
Blood for local Renal Panel	Follow instructions for local lab	Send to designated local lab	Local Lab	1.5		1.5	1.5
Serum for Biological Repository	(1) 3.0-6.0 (mL) ^e in tiger top SST ^b or (1) 5.0-10.0 (mL) ^e in tiger top SST ^b	1.5-5 mL serum frozen, shipped on dry ice (batched)	Biologic Repository		3<30kg 5≥30 kg	6<30kg 10≥30 kg	6<30kg 10≥30kg
Plasma for Biological Repository	(1) 3.0 (mL) ^e in PST ^f or 5.0 (mL) ^e in (2) PST ^f	1.5-2.5 mL plasma frozen, shipped on dry ice (batched)	Biologic Repository		3<30kg 5≥30 kg	3<30kg 5≥30 kg	3<30kg 5≥30kg
Serum for iPTH, hsCRP and Vitamin D	(1) 2.0 mL whole blood in tiger top SST ^b , transfer 0.5mL of serum for iPTH/hsCRP and 0.5 of serum for vitamin D into 2 red top cryovials	0.5 mL serum for iPTH/hsCRP and 0.5mL for vitamin D, frozen, shipped on dry ice (batched)	CBL		2.0		2.0
Plasma for FGF-23	(1) 1.0 mL whole blood in PST ^f , transfer 0.5 mL of plasma for FGF-23 into cryovial	0.5 mL plasma for FGF-23, frozen, shipped on dry ice (batched)	CBL		1		1
Whole blood for DNA	(3) 2.6 mL whole blood in yellow-top pediatric ACD tubes	Ship (3) 2.6 mL pediatric ACD tubes, room temp	Genetic Repository		7.8^g		7.8^g
TOTAL BLOOD COLLECTED (mL) (Includes PRN waste for iohexol determination)				10.5	16.8 <30kg 20.8 ≥30kg	20 <30kg 26 ≥30kg	25.3 <30kg 31.3 ≥30kg
TOTAL BLOOD COLLECTED (teaspoons)				≈ 4	≈ 3½ <30kg ≈ 4¼ ≥30kg	≈ 4 <30kg ≈ 5¼ ≥30kg	≈ 5¼ <30kg ≈ 6 ½ ≥30kg
TOTAL BLOOD COLLECTED (tablespoons)				≈ 1¼	≈ 1 <30kg ≈ 1½ ≥30kg	≈ 1 ½ <30kg ≈ 1 ¾ ≥30kg	≈ 1 ¾ <30kg ≈ 2¼ ≥30kg

^a CBL chemistries include: basic metabolic profile, phosphorous and albumin.

^b Invert SST 5 times gently to mix, stand SST upright to allow specimen to clot at room temp for 30 mins, centrifuge MAX SPEED (1100-1300 g) for 10 mins in swinghead units OR 15 mins in fixed angle units (balance tube in centrifuge).

^c In addition to other CBL chemistries, uric acid will be measured centrally starting at Visit 4 for Cohort 1 and starting at baseline for Cohort 2.

^d If initial serum for CBL chemistries is GROSSLY HEMOLYZED, collect 1.0mL of additional blood in a separate tube. If not grossly hemolyzed, do not collect additional blood.

^e 3.0 mL of whole blood yields 1.5 mL of plasma or serum; 6.0 mL yields 3.0 mL of plasma or serum; 5.0 mL yields 2.5 mL of plasma or serum and 10.0 mL yields 5.0 mL of plasma or serum.

^f **For plasma sample:** Invert PST 8-10 times gently, centrifuge at 1100-1300 g for 10 mins (swinghead unit) OR 15 mins (fixed angle unit). (No need to stand for 30 min.)

^g If inadequate samples of whole blood are collected at V1b, then additional whole blood should be collected and shipped at V3, V5 or V7.

Table 11.4b URINE SAMPLES

Types of Samples	Volumes of Samples	Shipping Requirements	Ship to	Samples Collected at Study Visits			
				V1a	V1b	V2 / V4 / V6 / V8 / V10 / V12 / V14	V3 / V5 / V7 / V9 / V11 / V13 / V15
Urine for CBL protein/creatinine/albumin	1 - 10 mL first morning urine ^a	1 – 10 mL in light blue top tube	CBL	1		1	1
Urine for local pregnancy	Follow instructions for local lab	Send to designated local lab	Local Lab	1		1	1
Urine for Biological Repository	(1) 15-60 (mL) fresh urine ^b in collection cup with protease inhibitor tablet(s), pour into centrifuge tube(s).	(7) 10 mL urine cryovials on dry ice (batched)	Biologic Repository		60	60	60
TOTAL URINE COLLECTED (mL)				2	60	62	62

^a At first morning void, collect 1-10 mL of urine to measure urine protein, creatinine and albumin.

^b Pour FRESH urine from initial collection cup into blue top collection cup with protease inhibitor tablets. Do not fill urine past the 60mL mark on the collection cup. One protease inhibitor tablet should be used for each 10-15mL of urine. Like all unused supplies, **unused tubes with protease inhibitors should be returned to CBL**. Close the top tightly to prevent leakage. Invert each collection cup gently 5-10 times. Protease inhibitor must be completely dissolved in urine. Once the protease inhibitor tablet is dissolved, pour urine into six (6) 10mL urine centrifuge tubes. (For each tube: remove the yellow top, pour urine into tube and screw cap back onto tube.) Place no more than 10 mL in each tube. Centrifuge urine tubes at 1100-1300 for 10 min (swinghead unit) OR 15 min (fixed angle unit). Supernates should be decanted into seven (7) 10mL urine cryovials. Pour no more than 9 mL of urine into each 10 mL urine cryovial and promptly freeze at -70°C.

Table 11.4c HAIR AND NAIL REPOSITORIES SAMPLES

Types of Samples ^a	Volumes of Samples	Shipping Requirements	Ship to	Samples Collected at Study Visits						
				V1a	V1b	V2	V3	V4	V5/V7/V9 / V11/V13/V15	V6/V8/V10/ V12/V14
Nail Clippings	1 mm from each fingernail/toenail (10 nail clippings)	Cryovial Nail clippers (stainless steel) / Room temperature	Biologic Repository		10 nail clippings			10 toenail clippings		
Hair Samples	≈ 20 fibers of hair ^{a,b}	Zip top bag (non-colored seal) Aluminum foil (standard) ½ g Silica Gel Desiccant bags with pellets Room temperature	Biologic Repository		≈ 20 hair fibers					
TOTAL HAIR AND NAIL SAMPLES COLLECTED					30			10		

^a Additional material to collect hair samples includes: stainless steel scissors and hair collection labels.

^b Powder free gloves should be worn when collecting hair samples.

LEGEND:
RED = CENTRAL BIOCHEMISTRY LABORATORY
GREEN = BIOSAMPLE REPOSITORY
ORANGE = GENETIC REPOSITORY
BLACK = LOCAL LABS

11.4.2 Samples and Volumes for Visits V1a, V1b, V2 through V15, and the Make-Up GFR.

VISIT 1a (Tests listed in order of priority if insufficient quantity of blood)

- 2 mL blood (1 mL serum) for CBL chemistries and iohexol blank (B0)
- 1 mL of additional blood for CBL (if initial sample is *GROSSLY hemolyzed*)
- 4 mL = (2) 1 mL blood for CBL iohexol Determination (waste 1 mL blood per draw if applicable)
- 1 mL blood (0.5 mL serum) for cystatin C
- 1 mL blood for local CBC
- 1.5 mL blood for local renal panel

TOTAL BLOOD VOLUME: 10.5 mL

(includes wasted blood prior to iohexol blood draws – only waste if applicable)

- Urine for local pregnancy (quantity per instructions from local lab)
- 1 mL first morning urine for CBL protein/creatinine

VISIT 1b (Tests listed in order of priority if insufficient quantity of blood)

- 2 mL blood (0.5 mL serum for iPTH, hsCRP and 0.5 mL serum for vitamin D)
- 1 mL blood (0.50 mL plasma for FGF-23)
- 7.8 mL whole blood in three pediatric ACD tubes for genetic repository
- 3 mL (< 30 kg) or 5 mL (>30 kg) blood in SST (1.5 – 2.5 mL serum in transport tube) for NIDDK biosample repository
- 3 mL (< 30 kg) or 5 mL (>30 kg) blood in PST (1.5 – 2.5 mL plasma in transport tube) for NIDDK biosample repository

TOTAL BLOOD VOLUME: 16.8 mL < 30kg OR 20.8 mL > 30kg

- 60 mL Urine for NIDDK biosample repository

VISIT 2 through 8 and subsequent even visits

(Tests listed in order of priority if insufficient quantity of blood)

- 2 mL blood (1 mL serum) for CBL chemistries and iohexol blank (B0)
- 1 mL of additional blood for CBL (if initial sample is *GROSSLY hemolyzed*)
- 4 mL = (2) 1 mL blood for CBL iohexol determination (waste 1 mL blood per draw if applicable)
- 1 mL blood (0.5 mL serum) for cystatin C
- 0.5 mL blood (0.25 mL serum) for CBL fasting lipid profile
- 1 mL blood for local CBC
- 1.5 mL blood for local renal panel
- 6 mL (< 30 kg) or 10 mL (>30 kg) Blood in SST (3 – 5 mL serum in transport tube) for NIDDK biosample repository
- 3 mL (< 30 kg) or 5 mL (>30 kg) blood in PST (1.5 – 2.5 mL plasma in transport tube) for NIDDK biosample repository

TOTAL BLOOD VOLUME: 20 mL < 30kg OR 26 mL > 30kg

(includes wasted blood prior to iohexol blood draws – only waste if applicable)

- Urine for local pregnancy (quantity per instructions from local lab)
- 1 mL first morning urine for CBL protein/creatinine/albumin
- 60 mL urine for NIDDK biosample repository

VISIT 3 through 7 and subsequent odd visits

(Tests listed in order of priority if insufficient quantity of blood)

- 1 mL blood (0.5 mL serum) for CBL chemistries
- *1 mL of additional blood for CBL (if initial sample is GROSSLY hemolyzed)*
- 2 mL blood (0.5 mL serum for iPTH, hsCRP and 0.5 mL serum for vitamin D)
- 1 mL blood (0.50 mL plasma for FGF-23)
- 1 mL blood (0.5 mL serum) for cystatin C
- 1 mL blood for local CBC
- 1.5 mL blood for local renal panel
- 6 mL (< 30 kg) or 10 mL (>30 kg) blood in SST (3 – 10 mL serum in transport tube) for NIDDK biosample repository
- 3 mL (< 30 kg) or 5 mL (>30 kg) blood in PST (1.5 – 2.5 mL plasma in transport tube) for NIDDK biosample repository
- *7.8 mL whole blood in three pediatric ACD tubes for genetic repository (if initial V1b sample is inadequate)*

TOTAL BLOOD VOLUME: 25.3 mL < 30kg OR 31.3 mL > 30kg

- 10 mL first morning urine for CBL protein/creatinine/albumin
- Urine for local pregnancy (quantity per instructions from local lab)
- 60 mL urine for NIDDK biosample repository

Make-Up GFR (V1a, V2, V3, V4, V5, V6, V7, V8 and subsequent visits)

- 2 mL blood (1 mL serum) for CBL chemistries and iohexol blank (B0)
- 1 mL blood (0.5 mL serum) for cystatin C
- For V1a, V2, irregular V3 and subsequent iohexol GFR study visits: (2) 1 mL blood draws for iohexol concentrations (waste 1 mL blood per draw if applicable) = 4 mL total

TOTAL BLOOD VOLUME: 7 mL

(includes wasted blood prior to iohexol blood draws – waste only if applicable)

- Urine for local pregnancy (quantity per instructions from local lab)

11.5 INSTRUCTIONS FOR COLLECTION AND SHIPMENT OF PRE-IOHEXOL INFUSION BLOOD DRAW

11.5.1 Preparation for Blood Draws

Iohecol based GFR Visits ONLY (V1a, V2 through V15) Prior to and Day of Visit

- For Visit 1a, encourage the participant to drink fluids (water or juice) throughout the visit.
- For Visits 2, 4, 6, 8 or subsequent iohecol GFR study visits when blood for a lipid profile will be drawn, instruct participants to fast but not thirst 10 hours prior to the visit. Recommend that they drink water or zero-calorie beverages (i.e., non-caffeinated diet drinks) and/or chew sugar-free gum. In special circumstances where fasting is difficult (i.e., long distance traveling), “clear” fluids with calories will be acceptable.
- Instruct the participant to continue taking their usual medication(s).
- Instruct the participants to bring their first morning urine to visit for protein and creatinine analysis.

The physician should order 5.0 mL (647 mg/mL) iohecol IV x1 from site-designated pharmacy and a topical anesthetic agent PRN. Iohecol solution is sensitive to light and therefore should be protected from exposure (i.e. wrapped in aluminum foil). Pre-infusion weight of syringe must be recorded without the foil on the appropriate Specimen Collection Form (L01, L21 or L41).

- Apply a topical anesthetic agent PRN
 - Apply a topical anesthetic agent to both arms (antecubital or other suitable veins) one half to one hour prior to placing the IV(s) (per instructions from pharmacy)
 - Topical anesthetic spray may be used PRN immediately prior to stick.
- Before iohecol infusion, obtain participant information (KID ID#, gender, height, weight and DOB) and take vitals: blood pressure, temperature, heart rate, and respiratory rate. Record information on Physical Examination Form (PE Form).
- Obtain the 5.0 mL prepared syringe of iohecol from site-designated pharmacy. The iohecol syringe should not be wrapped in foil during the infusion.
- Record pre and post iohecol infusion syringe weight on the appropriate Specimen Collection Form (L01, L21 or L41).

11.5.1.1 Labeling

Labels will be provided with each lab kit. Each tube will be pre-labeled with the participant’s ID number (KID ID), destination, specimen type and visit number. Using a waterproof marker, the date should be written on the label on the day of collection. To ensure that the writing does not smear, cover the written information with tape. Double check to be sure the numbers are clear and legible, and that the tubes (SST, PST and whole blood tubes) have not expired. Check that the date printed on the lower middle section of the BD manufacturer label as LOT#-YYYY-MM is equal to or later than the current month. For example, if the expiration date is XXXXXXXX-2006-01, the tube should not be used in February 2006.

11.5.1.2 Pre-Iohexol Infusion Blood Draw

There are two options for drawing the pre-iohexol infusion blood draw and three device options to use for the blood draw. Blood can be collected directly into the appropriate tubes or transferred into the appropriate tubes. The exact quantities of blood to be drawn will depend on the specific visit. See Table 11.4a.

NOTE: The pre-Iohexol blood draw **MUST** be drawn before the Iohexol infusion and the same access **CANNOT** be used for both Iohexol infusion and B1 (120 minutes after Iohexol infusion) and B2 (300 minutes after Iohexol infusion).

OPTION 1: Place two intravenous lines using 18-22 gauge polyethylene catheters at two separate vascular access sites. Blood can be drawn into two to three 10 mL syringes or into vacutainers. If using syringes, dispense the appropriate amount of blood into the specific tubes using an 18 gauge needle. If using a vacutainer, the blood should be drawn directly into the appropriate tubes.

OPTION 2: Place one butterfly (18 – 23 gauge) and one 18-22 gauge polyethylene catheter at two separate vascular access sites. Use tape to stabilize butterfly for Pre-Iohexol blood draw followed by Iohexol infusion. Blood can be drawn into two to three 10 mL syringes or vacutainers. If using syringes, dispense the appropriate amount of blood into the specific tubes using an 18 gauge needle. If using a vacutainer, blood should be drawn directly into the appropriate tubes

OPTION 3: Use separate butterfly needles for pre-iohexol blood draw and individual blood draw sticks. Use tape to stabilize butterfly for blood draw and infusion.

The tubes will be provided in the CBL kit. **REMEMBER: The visit will determine the amount of blood collected for specific tests and tubes needed.** Dispense blood into the tubes provided in the CBL kit:

- Tiger-top SST for iohexol blank (B0), CBL chemistries, cystatin C, lipid profile, hsCRP, iPTH, vitamin D and uric acid (beginning at V4 for Cohort 1 and at V1a for Cohort 2).
- SST for local renal panel is not provided in CBL kit.
- Lavender tube for local CBC is not provided in CBL kit. (NOTE: If participant has had a local CBC drawn within the past 30 days, the CBC results may be used instead of drawing another CBC. CBL studies blood draw amounts can be decreased by 1 mL).
- SST for optional* NIDDK Biosample Repository sample (same Tiger-top SST is used to collect blood for CBL chemistries, cystatin C, lipid profile, hsCRP & iPTH, vitamin D and uric acid)
- PST for FGF-23 is provided in CBL kit.
- (2) PST for optional* NIDDK Biosample Repository sample (same PST is used to collect blood for FGF-23)
- (3) ACD tubes for optional* Rutgers DNA repository

*The samples stored at the NIDDK and Rutgers DNA Repositories are optional and require consent from the participant and/or family.

If a butterfly is used to draw blood, the blood can be collected directly into the appropriate tubes.

Diagram 11.5a Procedures for pre-iohexol blood draw at Visit 1a

Diagram 11.5b Procedures for Visit 1b blood draw

Diagram 11.5c Procedures for Visit 2, 4, 6, 8 and subsequent even visit blood draw

Diagram 11.5d Procedures for Visit 3, 5, 7, 9 and subsequent odd visit blood draw

Diagram 11.5e Urine collection and processing procedures performed for urine samples that are sent to NIDDK BR

Sections 11.5.2 – 11.5.7 provide detailed instructions on processing each of the samples.

Diagram 11.5a Visit 1A Pre-Iohexol Infusion Blood Draw

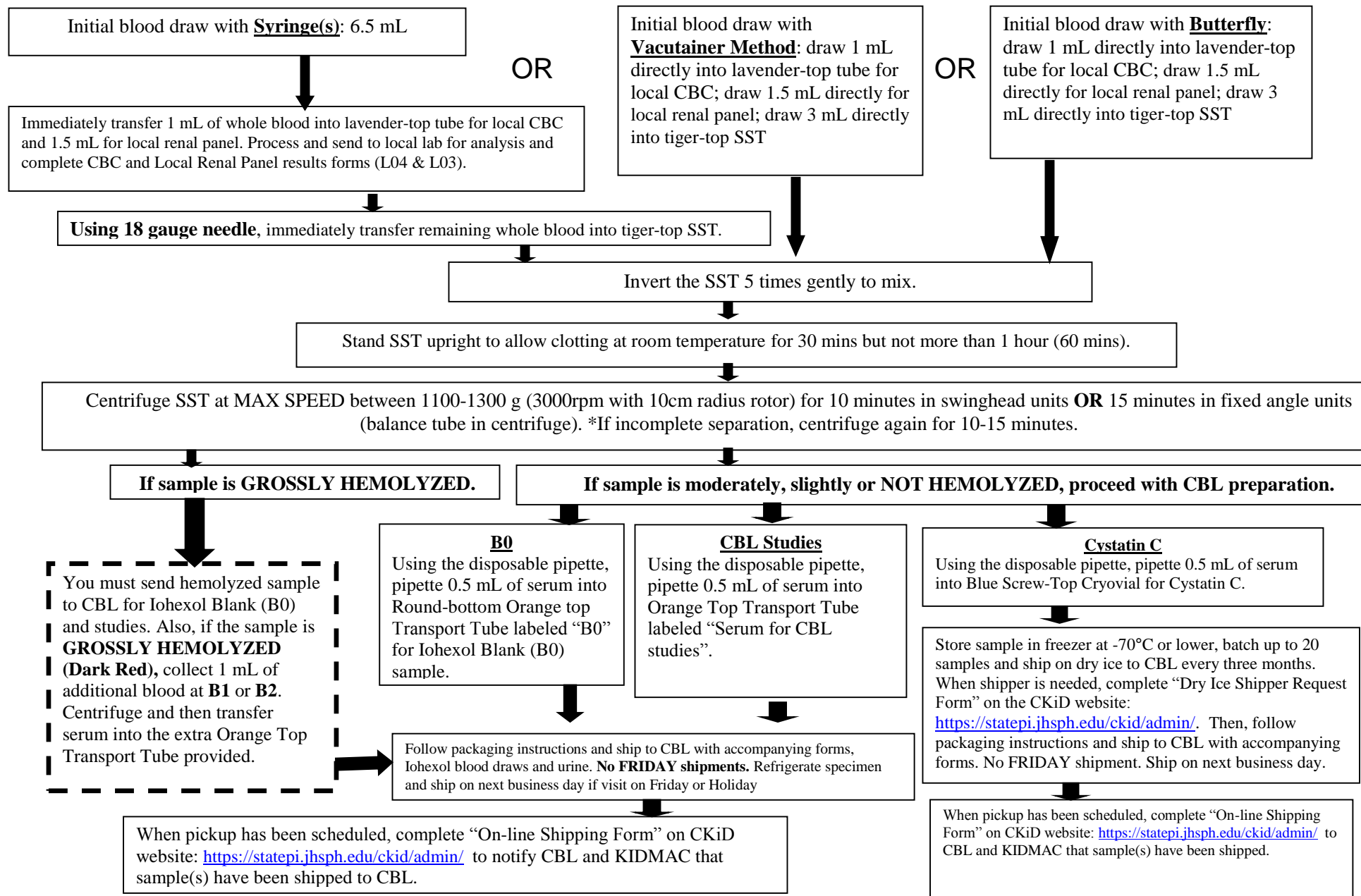


Diagram 11.5b Visit 1B Blood Draw

**For Initial Blood Draw with Syringe, Vacutainer OR Butterfly Method:
Select the Type of Consent Obtained (options 1 through 4) That Pertains to the CKiD Participant:
For irregular visits, an additional 1.0mL of blood should be collected in the Tiger Top SST for Iohexol Blank (B0) blood sample.**

1

If participant consented to both BIOLOGICAL AND GENETIC samples:

Collect 16.8 mL if participant is < 30 kg **OR** 20.8 mL if participant is ≥ 30 kg.

If < 30 kg, immediately transfer (using 18 gauge needle) or draw:

- 7.8 mL into (3) 2.6mL ACD tubes for Rutgers Genetic Repository (ACD Tubes must be COMPLETELY FILLED)
- 5 mL into (1) Tiger-Top SST for CBL and NIDDK Biosample Repository
- 4 mL into two (2) PSTs for CBL and NIDDK Biosample Repository

If ≥ 30 kg, immediately transfer (using 18 gauge needle) or draw:

- 7.8 mL into (3) 2.6mL ACD tubes for Rutgers Genetic Repository (ACD Tubes must be COMPLETELY FILLED)
- 7 mL into (1) Tiger-Top SST for CBL and NIDDK Biosample Repository
- 6 mL into two (2) PSTs for CBL and NIDDK Biosample Repository

2

If participant consented to BIOLOGICAL samples ONLY:

Collect 9 mL if participant is < 30 kg **OR** 13 mL if participant is ≥ 30 kg.

If < 30 kg, immediately transfer or draw:

- 5 mL into (1) Tiger-Top SST for CBL and NIDDK Biosample Repository
- 4 mL into two (2) PSTs for and CBL and NIDDK Biosample Repository

If ≥ 30 kg, immediately transfer or draw:

- 7 mL into (1) Tiger-Top SST for CBL and NIDDK Biosample Repository
- 6 mL into two (2) PSTs for CBL and NIDDK Biosample Repository

3

If participant consented to GENETIC samples ONLY:

Collect 10.8 mL from all participants (regardless of weight)

Immediately transfer or draw:

- 7.8 mL into (3) 2.6mL ACD tubes for Rutgers Genetic Repository (ACD Tubes must be COMPLETELY FILLED)
- 2 mL into (1) Tiger-Top SST for CBL
- 1 mL into (1) PST for CBL

4

If participant did NOT consent to BIOLOGICAL AND GENETIC samples:

Collect 3 mL from all participants (regardless of weight). Immediately transfer or draw 2 mL into (1) Tiger-Top SST for CBL and 1mL into PST for CBL.

Visit 1B Blood Draw Processing

PROCESSING BLOOD FOR CBL, NIDDK BR AND RUTGER SAMPLES

CBL & NIDDK BR (Serum)

Invert the Tiger Top SST 5 times gently to mix.

Stand SST upright to allow clotting at room temperature for 30 mins but not more than 1 hour (60 mins).

Centrifuge SST at MAX SPEED between 1100-1300g (3000rpm with 10cm radius rotor) for 10 mins in swinghead OR 15 mins in fixed angle. *If incomplete separation, centrifuge again 10-15 mins.

NIDDK (Serum)

Pipette 1.5mL (<30kg) or 2.5mL (≥30kg) serum into clear top cryovial (use different pipettes for serum and plasma).

**If there is any extra serum, then pipette the extra serum into the clear top cryovial marked "NIDDK BR SERUM".*

Store sample(s) in freezer at -70°C or lower, batch up to 40 samples and ship every three months (preferably during **January, April, July and October**). When shipper is needed, complete "NIDDK BR Shipper Request Form" on the CKiD website: <https://statepi.jhsph.edu/ckid/admin/>. Then, follow packaging instructions.

When pickup has been scheduled, complete "On-line Shipping Form" on CKiD website to notify the appropriate personnel from the NIDDK BR.

iPTH/hsCRP

Pipette 0.5 mL of serum into a red-top cryovial tube for CBL iPTH &, hsCRP

Vitamin D

Pipette 0.5 mL of serum into a red-top cryovial for CBL Vitamin D

Store sample in freezer at -70°C or lower and batch up to 20 samples and ship every three months (preferably during the months of **January, April, July and October**). When shipper is needed, complete "CBL Dry Ice Shipper Request Form" on the CKiD website: <https://statepi.jhsph.edu/ckid/admin/>. Then, follow packaging instructions and ship to CBL with accompanying forms. No FRIDAY shipments.

When pickup has been scheduled, complete "On-line Shipping Form" on CKiD website to notify CBL and KIDMAC that sample(s) have been shipped to CBL.

CBL & NIDDK BR (Plasma)

Invert each PST 8-10 times gently to mix.

Centrifuge each PST at MAX SPEED between 1100-1300g for 10 mins (swinghead) OR 15 mins (fixed angle).

FGF-23

Pipette 0.5 mL of plasma into a green-top cryovial for CBL FGF-23

Pipette 1.5mL (<30kg) or 2.5mL (≥30kg) plasma into cryovial with green cap insert (use different pipettes for serum and plasma) .. **If there is any extra plasma, then pipette the extra plasma into the green cap insert cryovial marked "PLASMA (Extra)".*

Store sample(s) in freezer at -70°C or lower, batch up to 40 samples and ship every three months (preferably during the months of **January, April, July and October**). When shipper is needed, complete "NIDDK BR Shipper Request Form" on the CKiD website: <https://statepi.jhsph.edu/ckid/admin/>. Then, follow packaging instructions.

When pickup has been scheduled, complete "On-line Shipping Form" on CKiD website to notify the appropriate personnel from the NIDDK and KIDMAC that sample(s) have been shipped to NIDDK BR.

RUTGERS

Invert each of the 3 pediatric yellow-top ACD Tubes 6 times gently to mix blood with additives.

Keep tubes at room temperature. **DO NOT FREEZE OR CENTRIFUGE.**

Follow packaging instructions, complete RUCDR Collection Form and ship immediately to Rutgers Repository with accompanying forms. **Specimen can be shipped on Friday.**

Complete "On-line Shipping Form" on CKiD website to notify the appropriate personnel at Rutgers and KIDMAC that sample(s) have been shipped to Rutgers.

Diagram 11.5c EVEN Visits 2, 4, 6, 8... Blood Draw

For Initial Blood Draw with Syringe, Vacutainer OR Butterfly Method:
Select the Type of Consent Obtained (options 1 through 4) That Pertain to the CKiD Participant:

- 1** If participant consented to **BIOLOGICAL** samples:
Collect **15-16** mL if participant is < **30 kg** OR **21-22** mL if participant is \geq **30 kg**.

If < **30 kg**, immediately transfer (using **18 gauge needle**) or draw:

- 9.5 mL into (2) Tiger-Top SSTs for CBL & NIDDK BR
- 3 mL into (1) PST for NIDDK Biosample Repository
- 1 mL in lavender-top tube for local CBC
(*tube not provided in CBL kit*)
- 1.5 mL in appropriate tube (*not provided*) for local Renal Panel
- **1 mL of additional blood in SST for CBL (if initial sample is GROSSLY HEMOLYZED)**

If \geq **30 kg**, immediately transfer (using **18 gauge needle**) or draw:

- 13.5 mL into (2) Tiger-Top SSTs for CBL & NIDDK BR
- 5 mL into (2) PST for NIDDK Biosample Repository
- 1 mL in lavender-top tube for local CBC
(*tube not provided in CBL kit*)
- 1.5 mL in appropriate tube (*not provided*) for local Renal Panel
- **1 mL of additional blood in SST for CBL (if initial sample is GROSSLY HEMOLYZED)**

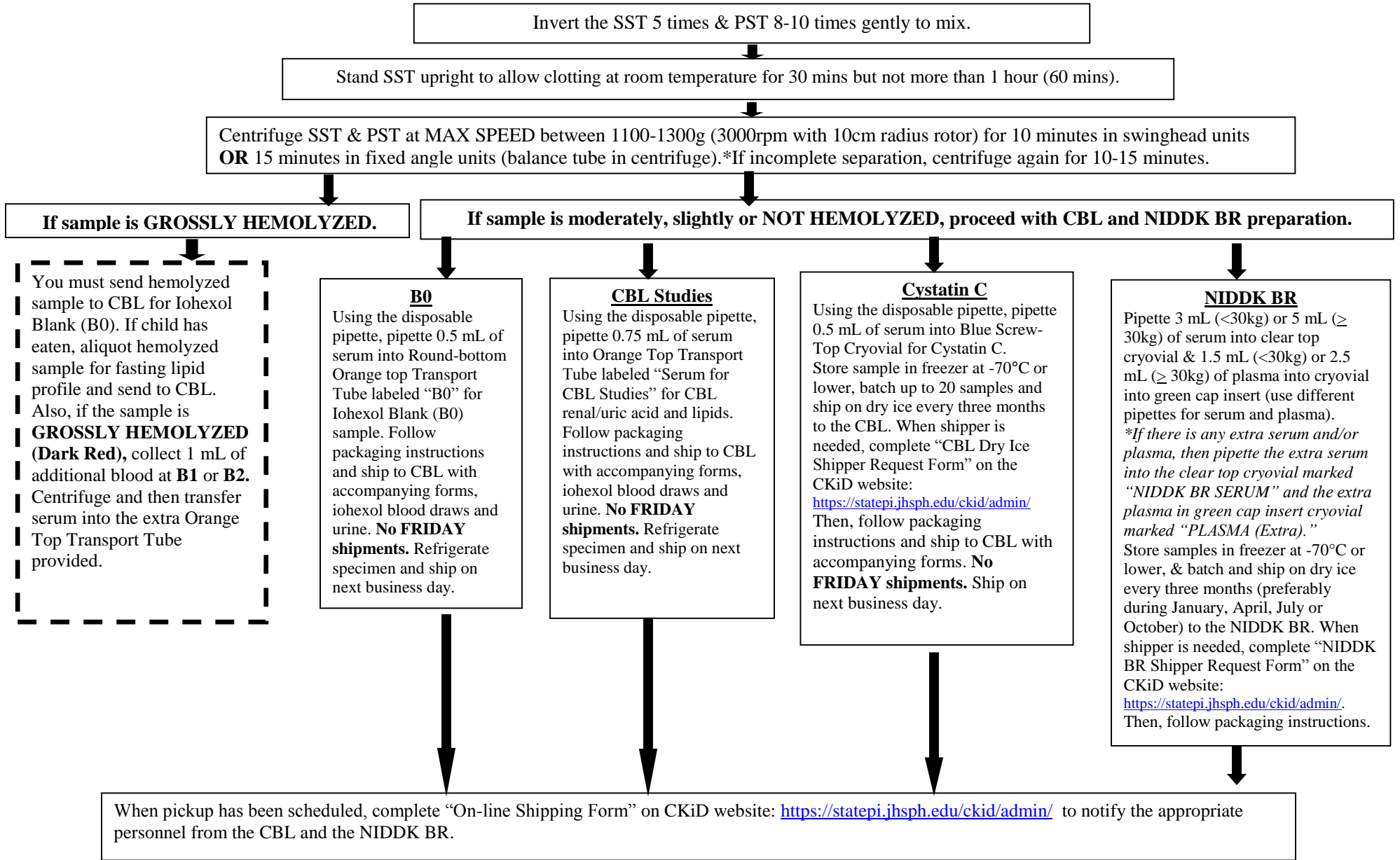
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- 2** If participant did **NOT** consent to **BIOLOGICAL** samples:
Collect **6-7** mL from all participants (regardless of weight) as specified below.

Immediately transfer (using 18 gauge needle) or draw:

- 3.5 mL into (2) Tiger-Top SSTs for CBL
- 1 mL in lavender-top tube for local CBC (*tube not provided in CBL kit*)
- 1.5 mL in appropriate tube (*not provided*) for local Renal Panel
- **1 mL of additional blood in SST for CBL (if initial sample is GROSSLY HEMOLYZED)**

EVEN Visits 2, 4, 6, 8... Blood Draw Processing

PROCESSING BLOOD FOR CBL & NIDDK BR



For Initial Blood Draw with Syringe, Vacutainer OR Butterfly Method:

Diagram 11.5d ODD Visits 3, 5, 7... Blood draw Select the Type of Consent Obtained (options 1 through 3) That Pertain to the CKiD Participant:

ONLY collect whole blood for Genetic Repository, if sample was not collected at V1b or sample collected at V1b was inadequate.

For irregular visits, an additional 1.0mL of blood should be collected in the Tiger Top SST for Iohexol Blank (B0) blood sample.

If participant consented to both BIOLOGICAL AND GENETIC samples:

1 Collect **24.3-25.3 mL** if participant is **< 30 kg** OR **30.3-31.3 mL** if participant is **≥ 30 kg**.

If **< 30 kg**, immediately transfer (using **18 gauge needle**) or draw:

- If not collected at V1b - 7.8 mL into (3) 2.6mL ACD tubes for Rutgers Genetic Repository (ACD Tubes must be **COMPLETELY FILLED**)
- 10 mL into (2) Tiger-Top SST for CBL and NIDDK Biosample Repository
- 4 mL into two (2) PSTs for CBL and NIDDK Biosample Repository
- 1 mL in lavender-top tube for local CBC (tube not provided in CBL kit)
- 1.5 mL in appropriate tube (*not provided*) for local Renal Panel
- **1 mL of additional blood in SST for CBL (if initial sample is grossly hemolyzed)**

If **≥ 30 kg**, immediately transfer (using **18 gauge needle**) or draw:

- If not collected at V1b - 7.8 mL into (3) 2.6mL ACD tubes for Rutgers Genetic Repository (ACD Tubes must be **COMPLETELY FILLED**)
- 14 mL into (2) Tiger-Top SST for CBL and NIDDK Biosample Repository
- 6 mL into two (2) PSTs for CBL and NIDDK Biosample Repository
- 1 mL in lavender-top tube for local CBC (tube not provided in CBL kit)
- 1.5 mL in appropriate tube (*not provided*) for local Renal Panel
- **1 mL of additional blood in SST for CBL (if initial sample is grossly hemolyzed)**

2 **If participant consented to BIOLOGICAL samples ONLY:**

Collect **16.5-17.5 mL** if participant is **< 30 kg** OR **22.5-23.5 mL** if participant is **≥ 30 kg**.

If **< 30 kg**, immediately transfer (using **18 gauge needle**) or draw:

- 10 mL into (2) Tiger-Top SSTs for CBL & NIDDK BR
- 4 mL into two (2) PSTs for CBL and NIDDK Biosample Repository
- 1 mL in lavender-top tube for local CBC (tube not provided in CBL kit)
- 1.5 mL in appropriate tube (*not provided*) for local Renal Panel
- **1 mL of additional blood in SST for CBL (if initial sample is GROSSLY HEMOLYZED)**

If **≥ 30 kg**, immediately transfer (using **18 gauge needle**) or draw:

- 14 mL into (2) Tiger-Top SSTs for CBL & NIDDK BR
- 6 mL into (2) PST for CBL and NIDDK Biosample Repository
- 1 mL in lavender-top tube for local CBC (tube not provided in CBL kit)
- 1.5 mL in appropriate tube (*not provided*) for local Renal Panel
- **1 mL of additional blood in SST for CBL (if initial sample is GROSSLY HEMOLYZED)**

3 **If participant consented to GENETIC samples ONLY, collect 15.3-16.3 mL from all participants** (regardless of weight):

Immediately transfer or draw:

- If not collected at V1b - 7.8 mL into (3) 2.6mL ACD tubes for Rutgers Genetic Repository (ACD Tubes must be **COMPLETELY FILLED**)
- 4mL into (2) Tiger-Top SST for CBL
- 1 mL into PST for CBL
- 1 mL in lavender-top tube for local CBC (tube not provided in CBL kit)
- 1.5 mL in appropriate tube (*not provided*) for local Renal Panel
- **1 mL of additional blood in SST for CBL (if initial sample is GROSSLY HEMOLYZED)**

4 **If participant did NOT consent to BIOLOGICAL samples and Genetic samples:**

Collect **7.5-8.5 mL** from all participants (regardless of weight) as specified below.

Immediately transfer (using 18 gauge needle) or draw:

- 4 mL into (2) Tiger-Top SSTs for CBL
- 1 mL into PST for CBL
- 1 mL in lavender-top tube for local CBC (tube not provided in CBL kit)
- 1.5 mL in appropriate tube (*not provided*) for local Renal Panel
- **1 mL of additional blood in SST for CBL (if initial sample is GROSSLY HEMOLYZED)**

PROCESSING BLOOD FOR CBL, NIDDK BR AND RUTGER SAMPLES

CBL & NIDDK BR (Serum)

Invert the Tiger Top SST 5 times gently to mix.

Stand SST upright to allow clotting at room temperature for 30 mins but not more than 1 hour (60 mins).

Centrifuge SST at MAX SPEED between 1100-1300g (3000rpm with 10cm radius rotor) for 10 mins in swinghead OR 15 mins in fixed angle. *If incomplete separation, centrifuge again 10-15 mins.

You must send hemolyzed sample to CBL for. Also if the sample is **GROSSLY HEMOLYZED (Dark Red)**, then collect 1 mL of additional blood in a SST. Centrifuge and then transfer serum into the extra Orange Top Transport Tube provided.

If sample is moderately, slightly or NOT HEMOLYZED, proceed with CBL and NIDDK BR preparation.

NIDDK (Serum)
Pipette 3mL (<30kg) or 5mL (≥30kg) serum into clear top cryovial for NIDDK BR (use different pipettes for serum and plasma).
**If there is any extra serum, then pipette the extra serum into the clear top cryovial marked "NIDDK BR SERUM"*

iPTH/hsCRP
Pipette 0.5 mL of serum into a red-top cryovial tube for CBL iPTH & hsCRP

Vitamin D
Pipette 0.5 mL of serum into a red-top cryovial for CBL Vitamin D

Cystatin C
Using the disposable pipette, pipette 0.5 mL of serum into Blue Screw-Top Cryovial for Cystatin C.

FGF-23
Pipette 0.5 mL of plasma into a green-top cryovial for CBL FGF-23

Store sample in freezer at -70°C or lower, batch up to 40 samples and ship during **Jan, Apr, Jul and Oct**. When shipper is needed, complete "NIDDK BR Shipper Request Form" on CKiD website: <https://statepi.jhsph.edu/ckid/admin/> Then, follow packaging instructions.

Store sample in freezer at -70°C or lower and batch up to 20 samples and ship every three months (preferably during the months of **January, April, July and October**). When shipper is needed, complete "CBL Dry Ice Shipper Request Form" on the CKiD website: <https://statepi.jhsph.edu/ckid/admin/> Then, follow packaging instructions and ship to CBL with accompanying forms. **No FRIDAY shipments.** Ship on next business day.

When pickup has been scheduled, complete "On-line Shipping Form" on CKiD website to notify the appropriate personnel for NIDDK BR and KIDMAC that sample(s) have been shipped to NIDDK BR.

When pickup has been scheduled, complete "On-line Shipping Form" on CKiD website to notify CBL and KIDMAC that sample(s) have been shipped to CBL.

NIDDK BR (Plasma)

Invert each PST 8-10 times gently to mix.

Centrifuge each PST at 1100-1300g for 10 mins (swinghead) OR 15 mins (fixed angle).

Pipette 1.5mL (<30kg) or 2.5mL (≥30kg) plasma into cryovial with green cap insert (use different pipettes for serum and plasma).
**If there is any extra plasma, then pipette the extra plasma into the green cap insert cryovial marked "PLASMA (Extra)".*

Store sample in freezer at -70°C or lower, batch up to 40 samples and ship during the months of **Jan, April, July and Oct**. When shipper is needed, complete "NIDDK BR Shipper Request Form" on the CKiD website: <https://statepi.jhsph.edu/ckid/admin/> Then, follow packaging instructions.

When pickup has been scheduled, complete "On-line Shipping Form" on CKiD website to notify the appropriate personnel from NIDDK BR and KIDMAC that sample(s) have been shipped to NIDDK BR.

RUTGERS

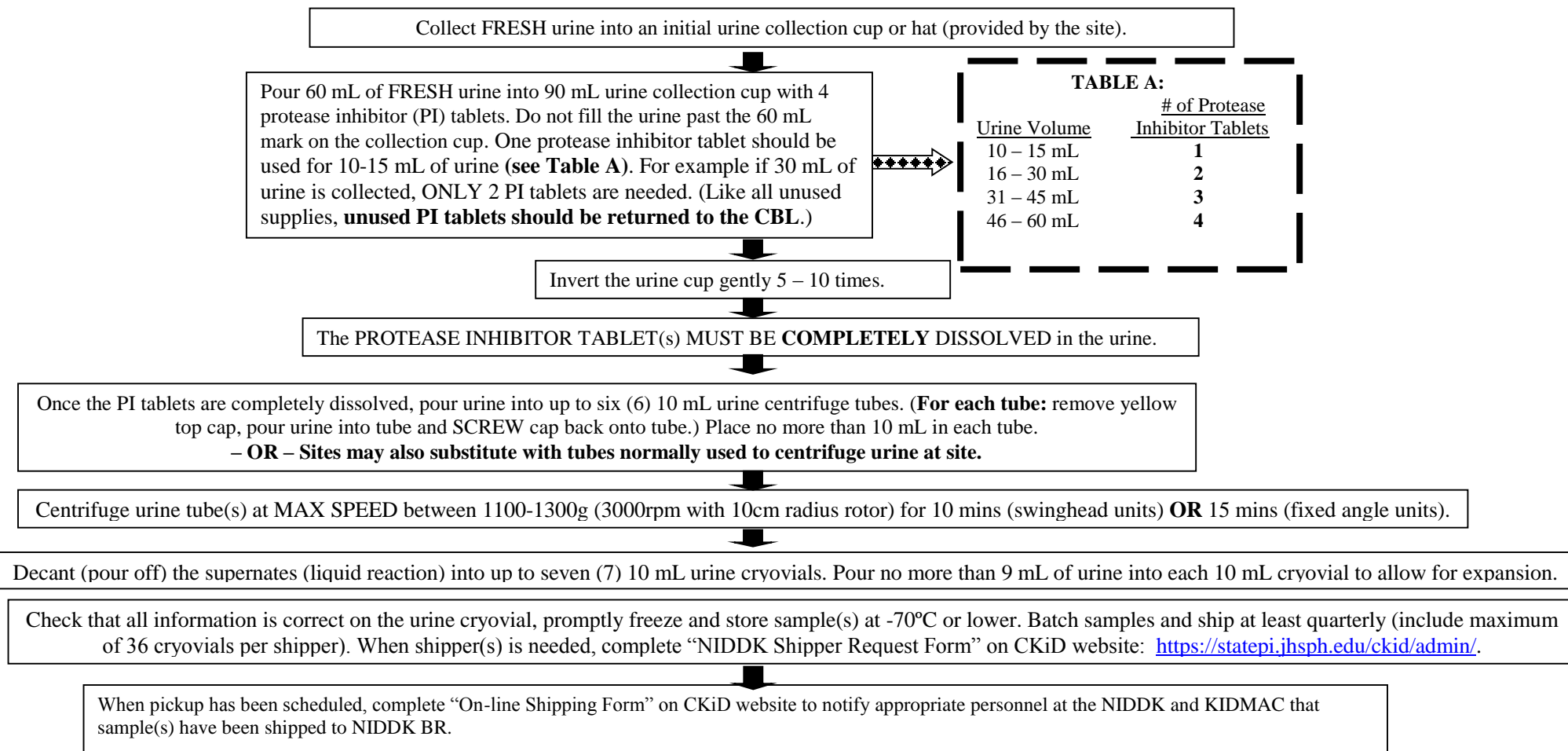
Invert each of the 3 pediatric yellow-top ACD Tubes 6 times gently to mix blood with additives.

Keep tubes at room temperature. **DO NOT FREEZE OR CENTRIFUGE.**

Follow packaging instructions, complete RUCDR Collection Form and ship immediately to Rutgers Repository with accompanying forms. **Specimen can be shipped on Friday.**

Complete "On-line Shipping Form" on CKiD website to notify the appropriate personnel at Rutgers and KIDMAC that sample(s) have been

Diagram 11.5e Urine Collection and Processing for NIDDK Biosample Repository (Visits 1b, 2, 3, 4, 5, 6, 7, 8 ...)



11.5.2 Instructions for Collection and Shipment of Biochemistries to CBL at room temperature

After the visit-specified volume of blood is collected in tiger top SST, complete appropriate Specimen Collection Form and perform the following:

1. After filling the tiger top SST tube(s) to designated amount, invert the SST 5 times gently to mix.
2. Stand SST upright to allow specimen to clot at room temperature for 30 minutes and not more than one hour (60 mins).
3. Centrifuge SST at MAX SPEED (between 1100-1300 g) for 10 minutes in swinghead units OR 15 minutes in fixed angle units (balance tube in centrifuge). If incomplete separation, centrifuge again for 10-15 minutes.
4. For all iohexol study visits, if initial serum sample is GROSSLY HEMOLYZED, pipette 0.5 mL serum into clear-top with red ring transport tube labeled "B0 serum" for CBL Iohexol Blank. Pipette remainder of hemolyzed serum into orange top transport tube labeled "serum for CBL studies". At a later time point, collect an additional 1 mL of blood in SST, centrifuge and transfer the serum into the extra orange top tube labeled "use for repeat serum...." For visits 3, 5, 7 or subsequent odd visits, if initial serum is GROSSLY HEMOLYZED, site does not have to repeat blood draw. Site should send hemolyzed samples to CBL in appropriately labeled orange top transport tubes.
5. Place the orange top transport tubes in the absorbent sleeve. **PLEASE MAKE SURE THAT CAP ON TUBE IS SECURE. IF NOT, SAMPLE MAY LEAK DURING TRANSPORT.**
6. **Use parafilm to around cap to help prevent the possibility of a leak.**
7. Place specimen into IATA-compliant shipping bag with absorbent gel pad and seal.
8. Place specimen into ambient IATA-compliant shipping box for shipment.
9. Place appropriate forms in the shipping box (i.e. Shipment Tracking Form, Confirmation of Written Consent)
10. After all CBL samples have been placed in shipping box, remove adhesive tape and seal.
11. Please use the pre-printed Fed Ex air bill provided in the kit. For international shipments, a pro forma must be completed.
12. Ship all CBL samples by Fed Ex, standard overnight delivery, to the CBL address. Call Fed Ex, 1-800-GO-FEDEX (1-800-463-3339). Give them the account number and the zip code of YOUR pickup address. FedEx will dispatch a courier to pick up the package. **Do not send samples so that they would arrive on a weekend, i.e., DO NOT SHIP ON FRIDAYS.** Samples collected on Friday should be refrigerated over the weekend and shipped on the next business day (i.e., Monday) to the CBL.
13. When you have scheduled the pickup, complete the "On-line Shipping Form" on the CKiD website: <https://statepi.jhsph.edu/ckid/admin>.

To obtain results of renal panel from the Nephron website:

- Go to <https://statepiaps.jhsph.edu/nephron/groups/aspproc/>
- Type in username and password. (If sites do not have or cannot locate their site's username and password, contact Judith Jerry-Fluker at jjerry@jhu.edu).
- Once on the Nephron website, click on "Report Menu." Then choose, "Selected Renal Panel Lab."

11.5.3 Instructions for Collection and Processing Lipid Profile Sample

- At Visits 2, 4, 6 & 8 when blood is drawn for lipid profile, the participant should be fasting, but not thirsting (participant may drink water or zero-calorie beverages (i.e., non-caffeinated diet drinks) and/or chew sugar-free gum up to the time of study), at least 10 hours prior to blood draw. Send serum to CBL even if it is hemolyzed (see section 11.4)
 1. Of the blood collected at pre-iohexol infusion blood draw in the tiger top SST; 0.25 mL serum should be reserved for the lipid panel.
 2. Pipette 0.25 mL serum into orange top transport tube for lipid profile. Note: Additional serum will also be added to the transport tube for other CBL chemistries and another cryovial for Cystatin C depending upon the visit.)
 3. Place orange top transport tubes in the absorbent sleeve. **PLEASE MAKE SURE THAT CAP ON TUBE IS SECURE. IF NOT, SAMPLE MAY LEAK DURING TRANSPORT.**
 4. **Use parafilm around cap to help prevent the possibility of a leak.**
 5. Place specimen in IATA-compliant shipping bag with absorbent gel pad and seal.
 6. Place specimen into ambient shipper for shipment and follow step 8-11 outlined in Section 11.5.2.

To obtain results of lipid panel from the Nephron website:

- Go to <https://statepiaps.jhsph.edu/nephron/groups/aspproc/>
- Type in username and password. (If sites do not have or cannot locate their site's username and password, contact Judith Jerry-Fluker at jjerry@jhu.edu).
- Once on the Nephron website, click on "Report Menu." Then choose, "Lipid Lab Variables Report."

11.5.4 Instructions for Collection and Processing Cystatin C Serum Sample that is shipped on Dry Ice

1. Of the blood collected at pre-iohexol infusion blood draw in the tiger top SST; 0.5 mL serum should be reserved for cystatin C.
2. Pipette 0.5 mL into plastic blue screw-top cryovial provided. **PLEASE MAKE SURE THAT CAP ON TUBE IS SECURE. IF NOT, SAMPLE MAY LEAK DURING TRANSPORT.**
3. **Use parafilm around cap to help prevent the possibility of a leak.**
4. Freeze and store frozen cystatin C sample in a freezer at -70°C or below. Cystatin C should be batched and shipped every three months (preferably during months of **January, April, July or October**). It is more cost-effective to “batch” samples and send in one shipper (with the iPTH/hsCRP, vitamin D and FGF-23). Cystatin C in serum is stable for at least 3 days at approximately 4° C and at least 1 year in a freezer at -70°C. Since cystatin C samples be shipped on dry ice with iPTH, hsCRP, Vitamin D and FGF-23 samples, sites should ship samples as specified (i.e., every three months) and refrain from storing samples for long periods of time.
5. When ready to ship frozen specimens for cystatin C, complete “CBL Dry Ice Shipper Request Form” on the CKiD website: <https://statepi.jhsph.edu/ckid/admin/>. The CBL will mail you the Styrofoam shipping container. Procure dry ice from your institution.

As of June 2008, the cystatin C samples should be shipped to the CBL. Sites should follow the shipping procedures outlined in Section 11.5.5.

11.5.5 Instructions for Processing High Sensitivity CRP, Intact PTH and Vitamin D Samples

1. Of the blood collected in the tiger top SST(s); appropriate amount of serum should be reserved for all samples.
2. After filling the SST(s), gently invert the **SST tube 5 times**. Stand upright to allow specimen to clot at room temperature for 30 minutes but not more than 1 hour (60 mins).
3. Centrifuge SST at MAX SPEED between 1100-1300g (3000rpm with 10cm radius rotor) for 10 minutes in swinghead units OR 15 minutes in fixed angle units (balance tube in centrifuge). If incomplete separation, centrifuge again for 10 - 15 minutes. Keep sample upright at all times.
4. Pipette 0.5 mL serum into red top cryovial labeled “iPTH/hsCRP” and 0.5 mL serum into red top cryovial labeled “vitamin D.” Samples should be frozen promptly. If sample(s) is not immediately put in the freezer, place on ice.
5. Store specimens in a freezer at -70°C or below. Serum samples for iPTH/hsCRP and vitamin D should be batched and shipped every three months. It is more cost-effective to batch samples, and send in one shipper on dry ice (with Cystatin C and FGF-23). iPTH/hsCRP serum is stable for at least 2 days at approximately 4° C and at least 6 months in a freezer at -70°C.
6. When ready to ship frozen specimens for iPTH/hsCRP and vitamin D, complete “CBL Dry Ice Shipper Request Form” on the CKiD website: <https://statepi.jhsph.edu/ckid/admin/>. The CBL will mail you the Styrofoam shipping container. Procure dry ice from your institution

11.5.6 Instructions for Collection and Processing FGF-23

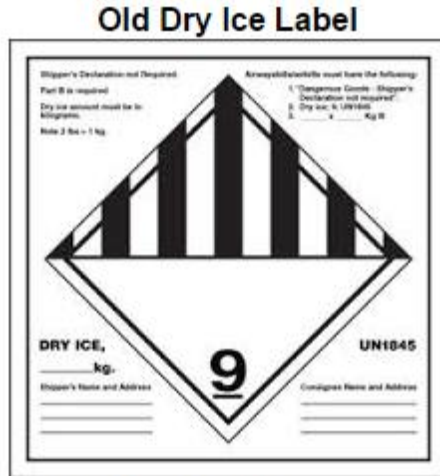
1. Draw blood in PST.
2. After filling the PST, gently invert the **PST tube 8 to 10 times** to mix the blood with the additives. Keep the tubes at room temperature. PST can be centrifuged immediately. (If site is unable to centrifuge PST immediately, it can be centrifuged when SST is centrifuged.)
3. Centrifuge (each) PST at MAX SPEED (between 1100-1300g) for 10 minutes in swinghead units OR 15 minutes in fixed angle units (balance tube in centrifuge). If incomplete separation, centrifuge again for 10 - 15 minutes.
4. Pipette 0.5 mL of plasma into a green-top cryovial labeled, "FGF-23."
5. If there is any extra plasma, then pipette the extra plasma into cryovial marked "PLASMA (Extra)."
6. Store tubes (specimens) in a freezer at -70°C or below. NIDDK BR plasma samples should be batched and shipped every three months (preferably during the months of **January, April, July and October**).

The new procedure for packaging and shipping the special frozen specimens to CBL for iPTH/hsCRP/vitamin D/FGF-23/Cystatin C is as follows:

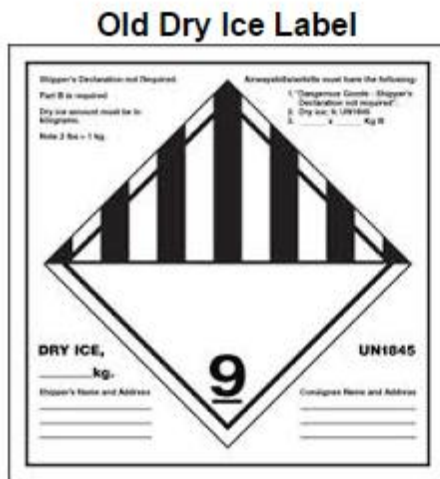
1. Remove specimens from the freezer. The CBL recommends that no more than 20 tubes be shipped in one batch. **Do not let the samples thaw.**
iPTH/hsCRP/vitamin D/FGF-23 and Cystatin C samples should be placed in separate IATA-compliant shipping bags (i.e. all iPTH samples in one bag, all hsCRP samples in another bag, etc.) and shipped in Dry Ice Shipper.
2. Plan to pick up dry ice as close to shipping time as possible to maximize its use.
3. Double check the KID ID and verify that the KID ID information on the cryovial matches that on the Specimen Shipment Tracking Form (ST05).
4. Place specimens in the IATA-compliant shipping bag(s) and seal.
5. Fill the Styrofoam container about half full of dry ice. **Reminder: dry ice is very cold and should be handled with insulated gloves.**
6. Place the IATA-compliant shipping bag(s) containing the specimens on the dry ice.
7. Fill the remaining space of the container with dry ice. **Do not tape the Styrofoam container closed,** as sublimation of dry ice to carbon dioxide gas will cause any airtight container to expand or possibly explode.
8. Please use the pre-printed Fed Ex air bills provided with the Styrofoam shipper. Remember to record the weight of the dry ice on the Fed Ex air bill as this information must be provided for all Fed Ex shipments containing dry ice.

9. EFFECTIVE 10/01/201: USDOT, IATA AND ICAO DISCONTINUED THE USE OF THE OLD DRY ICE LABELS WITH THE HORIZONTAL LINE. PLEASE SEE THE PICTURES BELOW OF THE OLD LABEL AND NEW LABEL:

CHANGE IN DRY ICE SHIPPING LABEL:



Please note labels not shown actual size.



Please note labels not shown actual size.



10. Call Fed Ex, 1-800-GO-FEDEX (1-800-463-3339). Give them the account number and the zip code of YOUR pickup address. FedEx will dispatch a courier to pick up the package.

11. Shipments to the CBL should be shipped on a Monday – Thursday (**NO FRIDAY SHIPMENTS**) via FedEx (Air bill provided in kit). When you have scheduled the pickup, complete the “Shipping Form” on the CKiD website: <https://statepi.jhsph.edu/ckid/admin> to notify the CBL and KIDMAC that sample(s) have been shipped to CBL.

- The preferred method for shipment of samples is to pack them in dry ice in an insulated container capable of retaining the coolant for the length of time to transport. It is currently

required that all individuals handling/shipping specimens on dry ice be trained and certified to ship “Dangerous Goods.” Sites should contact their local institutions regarding the availability of this training.

To obtain results of iPTH/hsCRP from the Nephron website:

- Go to <https://statepiaps.jhsph.edu/nephron/groups/aspproc/>
- Type in username and password. (If sites do not have or cannot locate their site’s username and password, contact Judith Jerry-Fluker at jjerry@jhu.edu).
- Once on the Nephron website, click on “Report Menu.” Then choose, “iPTH/hsCRP/vitamin D.”

Please note iPTH results collected prior to November 1, 2006 using serum collected and shipped at room temperature will be reported as “-9” to indicate that the result was deleted. However, future iPTH and hsCRP results will be reported in Nephron.

11.5.7 Example of Good Blood Sample Collection

**GOOD SAMPLE PREPARATION MEANS ACCURATE RESULTS:
USE THE INSIST METHOD**



- INVERT**gently, DO NOT SHAKE
- NOTE**.....any special handling instructions
- STAND**SST to clot 30 minutes
- INSPECT**.....tubes before centrifuging to assure a clot has formed
- SPIN**.....centrifuge SST as per instructions
- TRANSPORT**.....refrigerate/freeze sample as required. Follow shipping instructions

UNSPUN – clotted blood remains on top of gel barrier. Spin specimen in centrifuge for at least 15 minutes (this should be done no longer than 1 hour after drawing the specimen).

INCOMPLETE SEPARATION- serum is not completely separated from the red cells. Centrifuge again for 10-15 minutes. Cells left in serum can affect certain results.

INCOMPLETE SEPARATION- serum is not completely separated from the red cells. Centrifuge again for 10-15 minutes. Cells left in serum can affect certain results.

APPEARANCE OF HEMOLYSIS	
GROSSLY	Dark Red
MODERATELY	Red to Light Red
SLIGHTLY	Pink
NO HEMOLYSIS	Yellow

11.5.8 Collection procedure for Urine Sample (Protein Creatinine and Albumin)

For each study visit (V1a, V2, V3, V4, V5, V6, V7, V8, ...), the first morning urine samples **MUST** be collected in the specimen collection cup provided. A minimum of 1 mL of urine must be provided for accurate results for the protein, creatinine and albumin determination.

A few weeks prior to the participant's V1a, V2 - V8 and all subsequent visits, the clinical site coordinator should send a urine specimen collection cup and instruction sheet (see below) to the participant's caretaker with the urine specimen cup. Instructions entitled "Guidelines for the collection of a first morning urine sample" is to be included with the urine specimen collection cup shipment can be found on the CKiD website, Coordinator's Corner: <https://statepi.jhsph.edu/ckid/admin/coordinator/coordinator.html>
For any questions, or if more supplies are needed, please contact the Clinical Coordinating Centers Project Directors (Jackie Ndirangu Ndiranguj@email.chop.edu or Julie Starr jwstarr@cmh.edu), or the CBL (CKiDCBL@urmc.rochester.edu, 585-275-2434).

instruction sheet to accompany the urine container

Guidelines for the collection of a first morning urine sample

Enclosed you will find a urine cup. This will help you bring a "first-morning" urine sample to your CKiD visit. "First-morning" urine samples are the best way to measure protein in the urine. We think this might be important to look at in children with kidney problems.

This is how to collect a "first-morning" urine sample:

1. As soon as your child wakes up in the morning, please tell them to urinate ***into the cup provided***. This should be the ***FIRST*** thing your child does when he/she wakes up. For example, if feasible, he/she should not take a shower, get dressed or eat breakfast before giving the urine sample. ***DO NOT*** collect the urine into another container, and then transfer to the cup, if possible.
2. Ideally collect at least 1 teaspoon.
3. The urine cup can be placed into a bag if desired.
4. If your visit is greater than 1 hour from the time the urine sample is collected, please place the urine cup into the refrigerator until you leave for your visit. This will stop bacteria from growing in the urine, which may change the results.
5. Bring the urine cup to your visit and give it to the study coordinator.
 - If your child cannot urinate when he/she wakes up, just collect the urine sample into the cup provided when he/she is able to urinate.
 - If you forget to have your child urinate when he/she wakes up, just collect the urine sample into the cup provided when you or your child remember. Just let the study coordinator know it was not a "1st morning sample" when you arrive at your visit.
 - If your child catheterizes his/her bladder to empty it, still follow the instructions listed above. Just collect the urine from the catheter into the cup provided. This should be done when your child ***FIRST*** wakes up or is able to give a urine sample.

11.5.9 Instructions to Collect Repository Samples

11.5.9.1 NIDDK BR Biological Specimens

Plasma, serum and urine will be collected at Visit 1b, 2 - 15 and shipped to NIDDK BR. Hair and nail samples will be collected at Visit 1b only and toenails are collected at Visit 4 for Cohort 1. Detailed instructions on collecting and shipping hair and nail samples are described in Section 12. Collect specimens in appropriate containers.

Serum:

1. Pre-iohexol infusion blood draw in SST,
For V1b:
 - 3 mL – 5 mL of whole blood (depending on child’s weight: 3mL if < 30 kg; 5mL if > 30 kg) should be collected, reserving 1.5 mL – 2.5 mL of serum for NIDDK BR.
 - After the SST has been centrifuged (see 11.5.2), pipette 1.5 mL – 2.5 mL of serum (depending on child’s weight) into a clear top cryovial labeled, “serum.”**For subsequent follow-up visits beginning at V2:**
 - 6 mL – 10 mL of whole blood (depending on child’s weight: 6mL if < 30 kg; 10mL if > 30 kg) should be collected, reserving 3 mL – 5 mL of serum for NIDDK BR.
 - After the SST has been centrifuged (see 11.5.2), pipette 3 mL –5 mL of serum (depending on child’s weight) into a clear top cryovial(s) labeled “SERUM.”
2. If there is any extra serum, then pipette the extra serum into the additional clear-top cryovial marked “NIDDK BR SERUM.”
3. Store tubes (specimens) in a freezer at -70°C or below. NIDDK BR serum samples should be batched and shipped every three months (preferably during the months of **January, April, July and October**).

Plasma:

7. Draw blood in PST for NIDDK BR.
 - 3.0 mL of whole blood in one PST or 5.0 mL of whole blood in two PSTs (depending on child’s weight: 3mL if < 30 kg; 5mL if > 30 kg) into a PST.
8. After filling the PST, gently invert the **PST tube 8 to 10 times** to mix the blood with the additives. Keep the tubes at room temperature. PST can be centrifuged immediately. (If site is unable to centrifuge PST immediately, it can be centrifuged when SST is centrifuged.)
9. Centrifuge (each) PST at MAX SPEED (between 1100-1300g) for 10 minutes in swinghead units OR 15 minutes in fixed angle units (balance tube in centrifuge). If incomplete separation, centrifuge again for 10 - 15 minutes.
10. Pipette 1.5 mL – 2.5 mL of plasma (depending on child’s weight: 1.5 mL if < 30 kg; 2.5 mL if > 30 kg) into a cryovial with green cap insert labeled, “PLASMA.”
11. If there is any extra plasma, then pipette the extra plasma into the green cap insert cryovial marked “PLASMA (Extra).”
12. Store tubes (specimens) in a freezer at -70°C or below. NIDDK BR plasma samples should be batched and shipped every three months (preferably during the months of **January, April, July and October**).

Urine collection:

1. Collect FRESH urine in urine collection cup or hat (provided by the clinical site).
2. Transfer **60 mL** of FRESH urine into blue top urine collection cup with protease inhibitor tablets. **Do not fill the urine past the 60mL mark on the collection cup.** One protease inhibitor tablet should be used for each 10-15mL of urine. For example, if 30 mL of urine is collected, ONLY two (2) protease inhibitor tablets are needed. Like all unused supplies, tubes with unused protease inhibitor should be returned to CBL.

<u>Urine Volume</u>	<u># of Protease Inhibitor Tablets</u>
10 – 15 mL	1
16 – 30 mL	2
31 – 45 mL	3
46 – 60 mL	4

3. Secure top tightly to prevent leakage.
4. Invert urine cup gently 5-10 times.
5. The PROTEASE INHIBITOR TABLET MUST BE COMPLETELY DISSOLVED in urine.
6. Once the protease inhibitor tablet/s is/are dissolved, pour urine into six (6) 10 mL urine centrifuge tubes. (For each tube: remove yellow top cap, pour urine into tube and SCREW cap back onto tube.) Place no more than 10 mL in each tube. Sites may also substitute with tubes normally used to centrifuge urine at their site.
7. Centrifuge urine tubes at MAX SPEED (between 1100-1300g) for 10 minutes in swinghead units OR 15 minutes in fixed angle units (balance tube in centrifuge).
8. Decant (pour off) the supernate (liquid reaction) into seven (7) 10 mL urine cryovials. Pour no more than 9 mL of urine in each 10 mL cryovial to allow for expansion.
9. Check that all information is correct on the cryovials and promptly freeze at -70°C or below. NIDDK BR urine samples should be batched and shipped quarterly during the months of **January, April, July and October.**

Shipment to NIDDK Biosample Repository:

- When shipper is needed, complete the “NIDDK Shipper Request Form” on CKiD website: <https://statepi.jhsph.edu/ckid/admin>. The NIDDK Biosample Repository will mail you a shipper.
- Double check the KID ID on samples, and verify that the KID ID information matches that on the NIDDK Specimen Shipment Tracking Form (ST04). Follow the packaging instructions provided.
- Prepare shipments for FedEx pickup on Monday through Thursday. **NO FRIDAY SHIPMENTS, PLEASE.** The facility is not scheduled to be open on Saturday and Sunday when the package would be delivered. If there must be an exception, please coordinate with the NIDDK Repository before the close of business on Thursday.
- Assemble the package according to the instructions for the appropriate temperature of the shipment. Freeze specimens before the delivery because the specimens will be sent on dry ice. Urine must be frozen promptly at -70 degrees centigrade.

- Call Fed Ex, 1-800-GO-FEDEX (1-800-463-3339). Give them the account number and the zip code of YOUR pickup address. FedEx will dispatch a courier to pick up the package.
Ship samples to: Heather Higgins
Fisher Bioservices
20301 Century Blvd. Bldg 6. Suite 400
Germantown, MD 20874
- When pickup has been scheduled, complete “On-line Shipping Form” on CKiD website: <https://statepi.jhsph.edu/ckid/admin> to notify the appropriate NIDDK personnel and KIDMAC that sample(s) have been shipped to NIDDK BR
- **If you have questions, use the following contact information listed below.**

The NIDDK biological specimens’ repository is located at Fisher BioServices. Contact information is provided below.

Heather Higgins
Principal Investigator, BioServices
Fisher BioServices
20301 Century Blvd. Bldg. 6, Suite 400
Germantown, MD 20874

Phone: (240) 686-4703
Fax: (301) 515-4049
Mobile: (240) 793-0353
E-mail: BIO-NIDDKRepository@thermofisherSci.com

Sandra Ke, Assistant
Fisher BioServices
20301 Century Blvd. Bldg. 6, Suite 400
Germantown, MD 20874

Phone: (240) 686-4702
Fax: (301) 515-4049
Mobile: (301) 252-6214
E-mail: Sandra.Ke@thermofisherSci.com

Additional questions can be directed to the Judith Jerry-Fluker at the KIDMAC.

Judith Jerry-Fluker
KIDMAC Project Director
Bloomberg School of Public Health
Johns Hopkins University
615 N. Wolfe Street, E7007
Baltimore, MD 21205


Phone: (410) 614-1277
Fax: (410) 955-7587
E-mail: jjerry@jhu.edu

11.5.9.2 Rutgers Cell and DNA Specimen

Whole blood for Rutgers DNA Repository is a one-time sample and will be collected and shipped at V1b.

1. The RUCDR will supply all the blood vacutainer tubes and packaging material to be used.
2. Do NOT write the patient's name or any other personal identification information (e.g. SS#, DOB) on the vacutainers.
3. Of the blood collected at Visit 1B, 7.8 mL whole blood should be dispensed into three (3) 2.6mL pediatric yellow-top ACD tubes. **TUBES MUST BE COMPLETELY FILLED.** (Note: If inadequate samples are collected at V1b (or if unable to obtain sample), then additional whole blood should be collected and shipped at V3.)
4. Invert the tube gently 6 times to mix blood with additives and keep them at room temperature. **DO NOT CENTRIFUGE, REFRIGERATE OR FREEZE SAMPLE.**

Shipment to Rutgers DNA Repository:

1. Double check NIDDK ID #, verify that the ID on the tubes match the ID on the shipping tracking form (ST04).
2. Package the blood tubes in the safety mailer following the enclosed instructions. Be sure to seal the Styrofoam container with the red tape (water resistant).
3. Place the forms in the mailer box outside of the plastic bag. Tape cardboard box closed when assembly is complete.
4. **Complete "RUCDR Collection Form."** (See  **Appendix A)**. The information documented on this form is needed when the site completes the "On-line Shipping Form" on the CKiD website.



The image shows a 'RUCDR COLLECTION FORM' with the following details:

- DR. DOUGLAS FUGMAN: GENETICS**
RUCDR - NELSON LABS
604 ALLISON ROAD, (RM. C120A)
PISCATAWAY, NJ 08854-9082
- Form ID**
000061217
- https://rucdrfims.rutgers.edu**
Email: commstaff@biology.rutgers.edu
Phone: (732) 445-1498
Fax: (732) 445-1149

To Be Completed at Collection Site:

Subject Code: _____ Project: _____ Site: _____

Alternate ID: _____ () Male () Female Age: _____

Inventory ID - or - Subject Code for: _____ Family ID: _____
(purple should match the code on each tube) (pink form added)

TUBE 1: _____ TUBE 2: _____ Pedigree (If Applicable):
() Mother () Father
() Proband () Sibling
() Proband Tested Fragile-X Neg

TUBE 3: _____ TUBE 4: _____ Collection Date: ____/____/____

5. Use the enclosed FedEx shipping label to ship the sample to the Rutgers University Genetics Repository. Be sure shipping label is marked for priority overnight delivery.
6. For routine shipments be sure the outside of the box is labeled "Diagnostic Specimen Packed in Compliance with IATA Packaging Instruction 650."
7. Call Fed Ex, 1-800-GO-FEDEX (1-800-463-3339), and a courier will be dispatched to pick up the samples. Be sure to give Fed Ex the zip code of the PICKUP address, not that of the destination. The Rutgers Repository does allow Friday shipment. **Whole blood DNA samples collected on Friday can be shipped next day delivery to the Rutgers Repository.**

Ship Samples to: Dr. Douglas Fugman/Genetics
Rutgers Univ. Cell & DNA Repository
Div. Life Sciences-Nelson Labs
604 Allison Road (Rm C120A)
Piscataway, NJ 08854-8000

8. **Complete the "On-line Shipping Form" on the CKiD website:** <https://statepi.jhsph.edu/ckid/admin> to notify KIDMAC that sample(s) have been shipped to Rutgers. **KIDMAC or the appropriate CCC will notify Rutgers that samples have been shipped by using the STARLIMS system.**

Again, please note that sites should use the RUCDR Collection Forms that are included in the kits and discard any old versions of the form that they have!!!

These steps are completed by KIDMAC, the CCCs or the CBL personnel ONLY. Clinical sites should not perform these steps!

1. Configure your computer and obtain username and password.
 - Go to the following website, <http://www.rucdr.org/lims.htm>
 - Click on “Requirements” link on the left. Configure your computer according to these requirements. **This may require assistance from your IT department.**
 - Return to the original website, <http://www.rucdr.org/lims.htm> and click on “User Login” on the left.

This will bring you to the Starlims website where you can login using the username and password that was emailed to you.
(If you do not have a username and password click on the New User Request link at <http://www.rucdr.org/lims.htm>. If you have one, but have forgotten it, please contact Carrie Virgilio.)
 - If you are still unable to login please contact Rutgers dedicated Starlims helpdesk by email (starlimshelp@biology.rutgers.edu) or phone 732-445-4429 and they will assist you with getting access to the system.

2. Review Training videos.

Once you are able to logon please go to <http://www.rucdr.org/lims.htm> and click on the “Training Videos” link on the left. These training videos will show you how to Submit Samples. These videos are approximately two minutes each.

3. To request supplies follow the steps below. (Kits are requested by the CBL ONLY)
 - a) Go to the website: <http://www.rucdr.org/lims.htm>
 - b) Click on “User Login: on the left.
 - c) Enter username and password.
 - d) This will bring you to the Starlims website.
 - e) Click on “Request Supplies”

4. Notify Rutgers that samples were shipped (ONLY KIDMAC personnel notify Rutgers that samples have been shipped using STARLIMS. Sites complete the on-line shipping form on the CKiD website.)

- a) Go to the website: <http://www.rucdr.org/lims.htm>
- b) Click on “User Login: on the left.
- c) Enter username and password.
- d) This will bring you to the Starlims website.
- e) Click on “Sample Submission”
- f) Complete the “Project Information”
 - Submitter: **CSHIP**
 - Project: **NIDDK CKID**
 - Site: **NIDDK CKID 543**
 - Courier: **FedEx**
 - Tracking Number: Enter the Fedex Tracking Number CAREFULLY!!!

The screenshot shows a web form titled "Request for Sample Submission # 8391". Below the title is a step instruction: "Step 1: Please enter the Project information below". There is a "Video Help" link. The form is titled "Project Information" and contains the following fields:

- * Submitter: CSHIP
- * Project: NIDDK CKID (NIDDK)
- * Site: NIDDK CKID 543
- * Courier: FedEx
- * Tracking Number: A field with a pattern of slashes and numbers, indicating a tracking number.
- Note: An empty text area.

A note at the bottom states "(*) This is a mandatory field."

g) Click on “Manually add Samples to the list” and complete the “Details”

- Form #: Enter the FORM # that is documented on the RUDCR Collection Form
For example: 000061217
- Subject ID: Enter 543 before the KID
For example, KID 201077 would be entered as 543-201-007
- Alternate ID: Enter the KID ID
For example, KID 201077 would be entered as 201-007
- Family ID: LEAVE BLANK
- Pedigree: UNKNOWN
- Sex: Enter the GENDER of the participant
- Age: Enter the AGE of the participant and select YEARS from dropdown
- Date Collected: Enter the date the sample was collected
- *The “Subject ID” on the right is automatically populated*
- Complete the Inventory ID: Enter the BARCODE
For example: YC0003772
- Click “Add” and then “Save”

h) **For each vial, redo step “g”**

Once all of the data is entered, click “Submit Request”

The Rutgers DNA Repository is located at Rutgers University. Contact information is provided below.

Dale Heyward
Communications Coordinator

E-mail: heyward@biology.rutgers.edu

Carrie Virgilio
Communications Coordinator

Phone: 732-445-1498

E-mail: virgilio@biology.rutgers.edu

Additional questions can be directed to the Judith Jerry-Fluker at the KIDMAC.

Judith Jerry-Fluker
KIDMAC Project Director
Bloomberg School of Public Health
Johns Hopkins University
615 N. Wolfe Street, E7007
Baltimore, MD 21205

Phone: (410) 614-1277

Fax: (410) 955-7587

E-mail: jjerry@jhu.edu

11.6 INSTRUCTIONS FOR IOHEXOL INFUSION AND GFR BLOOD DRAWS

11.6.1 Protocol to Infuse Iohexol and Obtain Sample Collection for Determination of GFR

On the morning of the visit (or per site routine), the physician should order 5.0 mL (647 mg/ml) Iohexol IV x 1 and a topical anesthetic agent such as EMLA cream or LMX4 cream (PRN, if desired) from the site-designated pharmacy. The iohexol and topical anesthetic agent should be available when the subject arrives for the study visit. Document the syringe weight pre-iohexol infusion on the appropriate Specimen Collection Form (L01, L21 or L41). For both pre- and post-infusion weights, syringe should be weighed twice to ensure accuracy. Of note, the post-infusion weight should be at least 6.0 g less than the pre-infusion weight. Additionally, benadryl, epinephrine and solumedrol should be available in the event of a reaction to iohexol (estimated incidence of shock according to package insert for Omnipaque™ is 1 in 20,000).

Apply topical anesthetic agent PRN to two separate sites as directed prior to placing the IV(s) or IV and/or butterfly per instructions from pharmacy.

Place two intravenous lines (18-22 gauge polyethylene catheter) using two separate vascular access sites.

OR

Place one butterfly and one intravenous line (18-22 gauge polyethylene catheter) using two separate vascular access sites.

OR

Use separate butterfly needles for pre-iohexol blood draw and individual blood draw sticks.

Use tape to stabilize butterfly for blood draw and infusion (if using butterfly option). Butterfly can be used for iohexol infusion AFTER pre-Iohexol lab sample is obtained. (Provider(s) can also use a different acceptable vascular access.) The same access cannot be used for Iohexol infusion and collection of B1 and B2. **See Sections 11.5.2 – 11.5.7 for details on collecting, processing, and shipping pre-iohexol infusion blood draw.**

For accurate results, please note that the iohexol protocol should not be completed on the same day the participant is receiving certain other IV medications or contrast agents. For example, do not infuse iohexol on the same day the participant is receiving IV cytoxan. If the subject is scheduled to receive other IV medications the day of the iohexol infusion please consult with your respective CCC prior to the visit.

A physician should be immediately available (in person or by phone) during iohexol infusion (subject to local hospital practice)

1. Collect the pre-iohexol infusion blood draw.
2. **For V2/V4/V6/V8/V10/V12/V14:** after lipid profile is drawn, subject may resume eating and drinking beverages containing sugar (if desired).
3. Before infusing 5mL of iohexol, set timer to zero (time = zero). Simultaneously start timer and begin iohexol infusion. Infuse iohexol over 1-2 minutes. **LEAVE THE TIMER RUNNING THROUGHOUT THE IOHEXOL INFUSION AND THE POST-INFUSION BLOOD DRAWS. IF IOHEXOL IV OR BUTTERFLY INFILTRATES DURING THE INFUSION, THE STUDY MUST BE**

DISCONTINUED FOR THAT DAY. THE REPEAT VISIT SHOULD OCCUR AFTER 48 HOURS AND WITHIN THREE MONTHS OF INITIAL VISIT.

4. Flush with 10 mL normal saline solution to ensure that all Iohexol is infused into participant.
5. The iohexol IV or butterfly may be removed.
6. At Visit 1a/2 for Cohort 2 and Visits 4/6/8/10/12/14, obtain blood draw at 2 points.
7. Post infusion vitals should be taken approximately 10 minutes after the timer starts. (Note: This should be approximately 12-15 minutes after the start of iohexol infusion).
 - **IF A RASH DEVELOPS AFTER IOHEXOL INFUSION, CONSIDER IT A REACTION TO IOHEXOL AND NOTIFY PI IMMEDIATELY. CONSIDER ADMINISTERING 1 MG/KG BENADRYL IV (maximum dose: 50 mg Benadryl IV).**
 - **IN THE RARE EVENT THAT SYSTOLIC BLOOD PRESSURE DECREASES BY MORE THAN 25 mmHg, DIASTOLIC BLOOD PRESSURE DECREASES BY MORE THAN 20mmHG OR PULSE INCREASES BY MORE THAN 20 BEATS PER MINUTE, NOTIFY PI IMMEDIATELY TO EVALUATE THE REACTION. CONSIDER THE POSSIBILITY OF AN ANAPHYLACTIC REACTION TO IOHEXOL. CONSIDER ADMINISTERING 1 MG/KG BENADRYL IV (maximum dose: 50 mg Benadryl IV). DRAW UP 0.1 ML 1:1000 EPINEPHRINE FOR SUBCUTANEOUS INFUSION AND 2 MG/KGS SOLUMEDROL IV IF NECESSARY.**
 - **COMPLETE ADVERSE EVENTS FORM and send to the CCC for data entry.**
8. Weigh the post-iohexol infusion syringe on the same scale that the syringe was weighed pre-iohexol infusion and record weight on the appropriate Specimen Collection Form (L01, L21 or L41).
DO NOT FORGET TO RECORD WEIGHTS OF THE SYRINGE PRE AND POST IOHEXOL INFUSION ON THE SPECIMEN COLLECTION FORM L01, L21 or L41 BECAUSE THESE VARIABLES ARE CRITICAL FOR THE GFR CALCULATION.

DO NOT DRAW BLOOD FROM IV WHERE IOHEXOL WAS INFUSED; USE ALTERNATE ACCESS.
9. Remove 1 mL of blood (waste) and discard if using IV. (Note: if using IV with extension or piggyback tubing, follow hospital protocol for appropriate waste amount to ensure undiluted sample for all blood draws after iohexol infusion).
10. Draw 1 mL of blood into the appropriately pre-labeled SST at 120 and 300 minutes after Iohexol infusion (post-infusion). If using IV, flush with at least 3 mL saline (Note: follow hospital protocol for flushing for IV system used).

11. Record the time on the timer when blood draw is complete.

FOR ALL VISITS, RECORD THE EXACT TIME ON THE TIMER WHEN EACH BLOOD DRAW IS COMPLETED.

12. If blood draw is difficult with poor volume delivery, repeat draw 5 minutes later (or as soon as possible) and document this time on tube and appropriate Specimen Collection Form (L01, L21 or L41).

13. If using IV for B2, IV may be kept patent by using saline in IV or heparin flush (heparin concentration: 10 units/mL). **IF BLOOD DRAW USING IV IS IMPOSSIBLE, REPEAT WITH NEW VENIPUNCTURE.**

14. Following each blood draw, invert tube 5-10 times gently to mix.

15. Stand SST upright to allow the specimens to clot at room temperature for 30 minutes, but no longer than 1 hour.

16. Centrifuge SST at MAX SPEED between 1100-1300g (3000 rpm with 10cm radius rotor) for 10 minutes in swinghead or 15 minutes in fixed angle, to separate the cells from the serum.

17. Transfer serum into the cryovial labeled “B1 120 MINUTES” AND “B2 300 MINUTES.” **PLEASE MAKE SURE THAT ALL CAPS ON CRYOVIALS ARE SECURE. IF NOT, SAMPLE MAY LEAK DURING TRANSPORT.**

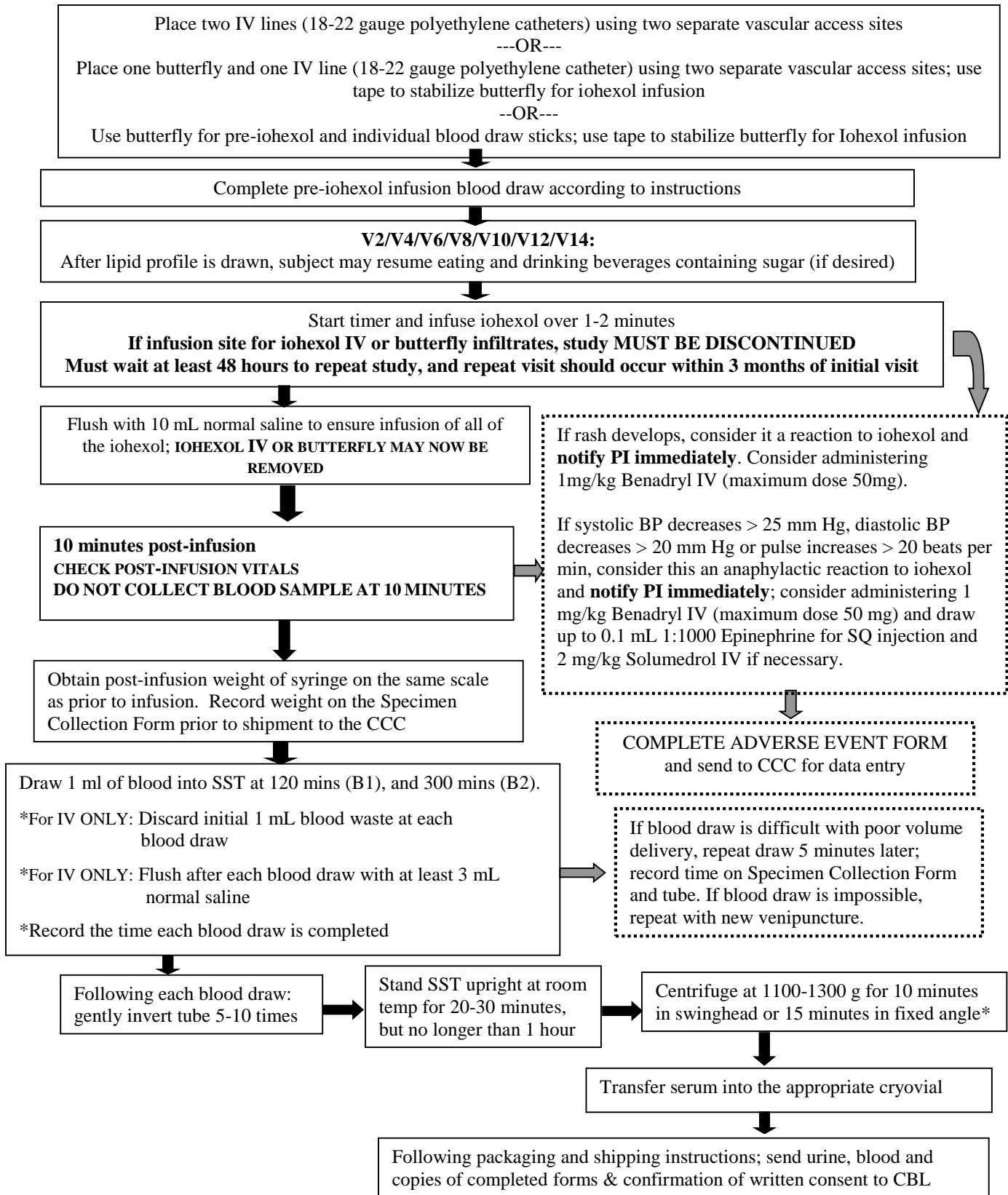
18. Use parafilm around cap to help prevent the possibility of a leak.

19. Package and send specimens to Paula Maier at the CBL using enclosed return Fed Ex label. Copy of Specimen Collection Form should be mailed to the CCC for data entry.

20. Shipping instructions are included in kit.

Diagram 11.6

Instructions for Iohexol Infusion and GFR Blood Draws



Physician should be immediately available (in person or by phone) during Iohexol Infusion
Encourage fluids throughout the visit.

*1100-1300 g = 3000 rpm with 10 cm radius rotor

11.7 SAMPLE STORAGE

CBL SAMPLES MUST NOT BE MAILED ON FRIDAY OR BEFORE HOLIDAYS as the University of Rochester receiving department is not open on weekends or holidays. If unable to ship specimens the same day as study, store in refrigerator (for samples that are not required to be frozen) and ship the next business day.

Upon receipt at the CBL, the iohexol specimens will be analyzed, and the remainder frozen at -70°C . Determinations of iohexol will be conducted in batches, with samples stored at -70°C at the CBL.

Serum specimens for renal panel, uric acid, lipid profiles, intact PTH, high sensitivity CRP, vitamin D, and cystatin C will be processed by the CBL.

Biological specimens for the NIDDK Biosample Repository should be frozen promptly and stored at -70°C until ready to be batched and shipped. Biologic specimens will be processed by NIDDK BR upon receipt. Samples must not be mailed on Friday or before holidays since there is no one available to receive and process samples at NIDDK BR on weekends or holidays.

Whole blood samples for Rutgers DNA Repository should be shipped on the day of collection and will be processed upon receipt. Rutgers will be able to accept samples if mailed on Friday.

11.8 RESULTS

Results of renal panel, lipid profile, urine protein, urine creatinine, iohexol-based GFR, estimated GFR, iPTH and hsCRP labs, are available on NEPHRON, the data management system, located at <https://statepiaps.jhsph.edu/nephron/groups/aspproc/>.

11.8.1 Alert/Panic Values

Alert and Panic values are meant to flag important deviations from the normal range. Because these blood samples have been drawn a considerable amount of time before the report is posted (e.g. time for shipping, etc.), they cannot and should not be used for standard of care purposes.

11.9 GENERAL INFORMATION

11.9.1 Storing Iohexol

Protect vials of Omnipaque from strong daylight and direct exposure to sunlight. Do not freeze.

Omnipaque should be stored at controlled room temperature, 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86).

The following is information on **managing peripheral infiltration of IV contrast**. Note the policy may be different at participating sites.

1. Stop the contrast infusion
2. Notify the responsible physician
3. Attempt to aspirate any remaining contrast out of the cannula before discontinuing.
4. Elevation of the extremity may be recommended on a case by case basis

For further instructions on storing Iohexol, see Section 11 – Appendices B (Omnipaque MSDS) and C (Omnipaque Prescribing Information).

11.9.2 Measurement of renal panel, lipid profile, intact PTH, high sensitivity CRP, vitamin D, uric acid, urine protein/creatinine/albumin, and iohexol.

The renal panel is measured on serum obtained from a SST. Sodium, potassium, chloride, and carbon dioxide are measured in mEq/L. Urea nitrogen, creatinine, calcium, glucose, and phosphorous are measured in mg/dL. Albumin is measured in gm/dL. Lipid profile is given in terms of mg/dL. These samples are obtained on a fasting (but not thirsting) blood sample. First morning urine is collected for protein and creatinine, both of which are measured in mg/dL so that the ratio is dimensionless. Iohexol is collected on samples obtained at 120 and 300 minutes after an infusion of 5 mL of iohexol (Omnipaque™). Iohexol is measured by high performance liquid chromatography (HPLC), and concentration is given in mcg/mL. Uric acid is measured in ng/CL.

11.9.3 Technical details for sample analysis

HPLC Instrumentation: Agilent 1100 HPLC system with variable wavelength UV detector.

Column: Zorbax Eclipse XBD-C8, 4.6 x 150 mm, 5 micrometer particle size (Agilent Technologies).
Chromatographic conditions: Isocratic elution at 1.0 mL/min with 20 mM potassium phosphate pH 2.5 and 4% acetonitrile, column maintained at 30 C, peaks monitored at 254 nm.

Renal Panel Instrumentation: Roche/Hi tachi 912/917/Modular analyzers, which includes enzymatic creatinine.

11.10 REFERENCE RANGES

Reference Ranges for the Central Biochemistry Laboratory (CBL)

<u>Serum</u>	Normal Range	Units
Sodium	133 – 145	mEq/L
Potassium	3.6 – 5.2	mEq/L
Chloride	96 – 108	mEq/L
Carbon dioxide	20 – 28	mEq/L
Urea Nitrogen	6 – 20	mg/dL
Creatinine:	0.5 – 1.00	mg/dL
Calcium	8.6-10.2	mg/dL
Glucose	60 – 99	mg/dL
Phosphorous	4.0-6.5	mg/dL
Albumin	3.5 – 5.2	g/dL
Intact PTH	15 – 65	pg/mL
High Sensitivity CRP	0 – 10	mg/L
Uric acid	3.1 – 9.2	mg/dL
FGF-23	13.3 – 19.0	pg/mL

Lipid Profile Reference Ranges

	<u>Risk Classification</u>						Units
	Low	Optimal	Near or Above Optimal	Borderline High	High	Very High	
LDL-Cholesterol		<100	100-129	130-159	160-189	>189	mg/dL
HDL-Cholesterol	<40				>60		mg/dL
			Desirable/ Normal	Borderline High	High	Very High	
Total Cholesterol			<200	200-239	>240		mg/dL
Triglycerides			<150	150-199	200-499	>500	mg/dL

Reference Ranges for Urine

	Range	Units
Creatinine	20-300	mg/dL
Protein	0-11	mg/dL
Microalbumin	<i>no range provided</i>	mg/dL

Reference Ranges for Cystatin C

	Range	Units
Cystatin C	0.53 – 0.95	mg/L

11.11 TEST CANCELLATION

Results for samples that are grossly hemolyzed may not be accurate for potassium, phosphate, albumin, or creatinine. In addition, reported non-fasting lipid panels will not be analyzed at the CBL. Sites are encouraged to inform the CBL if the participant did not fast.



RUCDR COLLECTION FORM

Ship at room temperature in Safety Mailer
Enclose this form with Sample Kit.

FORM #



DR. DOUGLAS FUGMAN; GENETICS
RUCDR - NELSON LABS
604 ALLISON ROAD. (RM. C120A)
PISCATAWAY, NJ 08854-8082

Form ID

000061217

<https://rucdr.lims.rutgers.edu>
Email: commstaff@biology.rutgers.edu
Phone: (732) 445-1498
Fax: (732) 445-1149

To Be Completed at Collection Site:

Subject Code: 543-2-01-077
KID

Project: CKID Site: 543

Alternate ID: 2-01-077
KID

Male Female Age: 15

Inventory ID - or - Subject Code for:
(number should match the barcode on each tube) (code from above)

Family ID: _____ *leave Blank*

TUBE 1: YC00003771 TUBE 2: YC00003772

Pedigree (If Applicable):

Mother Father

Proband Sibling

Proband Tested Fragile-X Neg

TUBE 3: _____ TUBE 4: _____

Collection Date: 05 / 23 / 2011

Courier#: Fedex

Collection Time: 15:48 (Please use military time) * *corresponds to 3:48 pm*

Contact the Rutgers Cell & DNA Repository through StarLIMS (<https://rucdr.lims.rutgers.edu>) or at commstaff@biology.rutgers.edu to convey package Tracking Number/Subject ID. If sample is shipped on a Friday for Saturday delivery, notify Rutgers and check FedEx form for Saturday delivery.

To be Completed by Rutgers University Cell & DNA Repository

Initial: _____

For RUCDR use only

Tube 1 Vol: ___ () ACD () EDTA () NaHep () PEDI () SP () S () PAX
 Tube 2 Vol: ___ () ACD () EDTA () NaHep () PEDI () SP () S () PAX
 Tube 3 Vol: ___ () ACD () EDTA () NaHep () PEDI () SP () S () PAX
 Tube 4 Vol: ___ () ACD () EDTA () NaHep () PEDI () SP () S () PAX

DATE SAMPLE RECEIVED:

Deviation Code:

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Product Name: Omnipaque®

Synonyms: Omnipaque® 140 mg I/ml, 180 mg I/ml, 210 mg I/ml, 240 mg I/ml, 300mg/ml and 350 mg I/ml Injection

Applications: Radiodiagnostic

Emergency Number: In an emergency, call 1-800-654-0118

Manufacturer: Amersham Health
101 Carnegie Center
Princeton, NJ 08540-9998
609-514-6000 or 1-800-654-0118

2. COMPOSITION/INFORMATION ON INGREDIENTS

<u>Ingredient Name</u>	<u>CAS No.</u>	<u>Percent by Weight</u>
Iohexol*	66108-95-0	> 25.0
Water	7732-18-5	> 25.0

* - Sterling Health Protection Guide:
5mg/m³ 8-hr TWA, 10mg/m³ STEL

3. HAZARDS IDENTIFICATION

***** **EMERGENCY OVERVIEW** *****

An aqueous solution. Presents little or no hazard if spilled or in fire.

WARNING: This is a pharmaceutical material available only with a prescription - use only as directed. Persons allergic to shellfish or iodine may be allergic to iohexol.

4. FIRST AID MEASURES

Eyes: In case of eye contact, flush eyes with plenty of water for at least 15 minutes. Seek medical attention if irritation develops.

Skin: Wash thoroughly with soap and water.

Ingestion: In case of overdosage, seek immediate medical attention or contact the Poison Control Center for further instructions.

Inhalation: Not an expected route of entry.

5. FIRE FIGHTING MEASURES

Flammable Properties: Nonflammable. This is an aqueous-based formulation.

Extinguishing Media: Use any extinguishing agent which is suitable for the surrounding fire.

Fire Fighting Procedures: Use normal fire fighting gear. Ventilate area - free flame may rupture container and decompose product to form toxic and irritating iodine vapors.

Unusual Fire and Explosion Hazards: None known

6. ACCIDENTAL RELEASE MEASURES

Spills: Contain the spill by placing paper towels or a suitable absorbent material around the edges of the spill and work inward. Carefully scoop up into a properly labeled waste container for disposal. Wash area of spill to remove from surfaces.

7. HANDLING AND STORAGE

Handling and Storage Precautions: Store away from heat and light - these conditions may produce iodine vapors. Keep this and all drugs out of the reach of children.

Work/Hygienic Practices: Use good personal hygiene - wash hands and exposed skin thoroughly with soap and water after use.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering controls: Normal ventilation

Eye/Face Protection: None normally required. Avoid eye contact.

Skin Protection: None normally required. Gloves should be worn to clean up spills.

Respiratory Protection: None normally required.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: Clear liquid

Color: Colorless to pale yellow

Solubility in Water: Soluble

Specific Gravity: Not applicable

10. STABILITY AND REACTIVITY

Stability: Stable

Conditions to Avoid: Exposure to flame or temperatures above 300 °F.

Materials to Avoid: None known

Hazardous Decomposition

Products: Iodine vapors

Hazardous

Polymerization: Will not occur

11. TOXICOLOGICAL INFORMATION

Subchronic (Target

Organ Effects): The following adverse reactions have been reported:

Central Nervous System: Vertigo (including dizziness and lightheadedness), pain, vision abnormalities (including blurred vision and photomas), headache, and taste perversion. Other including anxiety, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus were reported.

Gastrointestinal System: Nausea and vomiting. Others including diarrhea, dyspepsia, cramp, and dry mouth were reported.

Cardiovascular System: Arrhythmias including PVCs and PACs, angina/chest, pain and hypotension. Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported. In controlled clinical trials, involving 1485 patients, one fatality occurred. A cause and effect relationship between this death and iohexol has not been established.

Respiratory System: Dyspnea, rhinitis, coughing, and laryngitis.

Skin and Appendages: Urticaria, purpura, abscess, and pruritus.

Carcinogenicity: NTP: No, IARC: No, OSHA: No.

12. ECOLOGICAL INFORMATION

No data available

13. DISPOSAL CONSIDERATIONS

Disposal Methods: As of the MSDS revision date, this product does not meet the United States EPA definition of a hazardous waste. Dispose in accordance with local, state and federal regulations.

14. TRANSPORT INFORMATION

Proper Shipping Name: Non-regulated

15. REGULATORY INFORMATION

U. S. Federal Regulations:

This product does **not** contain any ingredients which are regulated on the U.S. EPA List of Toxic Chemicals (40 CFR 372) above the de minimus threshold, and is therefore not subject to release reporting under Section 313 of EPCRA.

16. OTHER INFORMATION

Revision Date: April 2003 (company name and emergency number)

Reference

Documentation: Primary references used in the preparation of this document:

1. Omnipaque® Package Insert
2. Omnipaque® MSDS (Sterling Winthrop)
3. ACGIH Guide to Occupational Exposure Values - 1991
4. Sterling Winthrop Corporate Quality Pharmaceutical File - 2/10/89

Disclaimer:

This information is furnished without warranty, representation, or license of any kind, except that it is accurate to the best of Amersham Health knowledge or obtained from sources believed to be accurate. Amersham Health does not assume any legal responsibility for use or reliance upon same. Customers are encouraged to conduct their own tests. Before using any product, read its label.

1163498 USA



GE Healthcare

ONC-10-CORK

OMNIPAQUE™
(iohexol) Injection



140 180 240 300 350

140 350 NOT FOR INTRATHECAL USE

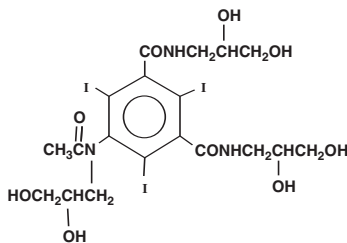
OMNIPAQUE in REDIFLO™ (prefilled cartridges) NOT FOR INTRATHECAL USE

Section I – Intrathecal
Section II – Intravascular
Section III – Oral/Body Cavity Use

R_x ONLY

DESCRIPTION

Iohexol, N,N' - Bis(2,3-dihydroxypropyl)-5-[N-(2,3-dihydroxypropyl)-acetamido]-2,4,6-triiodo-isophthalamide, is a nonionic, water-soluble radiographic contrast medium with a molecular weight of 821.14 (iodine content 46.36%). In aqueous solution each triiodinated molecule remains undissociated. The chemical structure is:



OMNIPAQUE is provided as a sterile, pyrogen-free, colorless to pale-yellow solution, in the following iodine concentrations: 140, 180, 240, 300, and 350 mgI/mL. OMNIPAQUE 140 contains 302 mg of iohexol equivalent to 140 mg of organic iodine per mL; OMNIPAQUE 180 contains 388 mg of iohexol equivalent to 180 mg of organic iodine per mL; OMNIPAQUE 240 contains 518 mg of iohexol equivalent to 240 mg of organic iodine per mL; OMNIPAQUE 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per mL; and OMNIPAQUE 350 contains 755 mg of iohexol equivalent to 350 mg of organic iodine per mL. Each milliliter of iohexol solution contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide. All solutions are sterilized by autoclaving and contain no preservatives. Unused portions must be discarded. Iohexol solution is sensitive to light and therefore should be protected from exposure.

The available concentrations have the following physical properties:

Concentration (mgI/mL)	Osmolality* (mOsm/kg water)	Osmolarity (mOsm/L)	Absolute Viscosity (cp)		Specific Gravity 37°C
			20°C	37°C	
140	322	273	2.3	1.5	1.164
180	408	331	3.1	2.0	1.209
240	520	391	5.8	3.4	1.280
300	672	465	11.8	6.3	1.349
350	844	541	20.4	10.4	1.406

* By vapor-pressure osmometry.

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OMNIPAQUE 140, OMNIPAQUE 180, OMNIPAQUE 240, OMNIPAQUE 300, and OMNIPAQUE 350 have osmolalities from approximately 1.1 to 3.0 times that of plasma (285 mOsm/kg water) or cerebrospinal fluid (301 mOsm/kg water) as shown in the above table and are hypertonic under conditions of use.

SECTION I

CLINICAL PHARMACOLOGY—Intrathecal

Iohexol is absorbed from cerebrospinal fluid (CSF) into the bloodstream and is eliminated by renal excretion. No significant metabolism, deiodination, or biotransformation occurs.

In five adult patients receiving 16 to 18 milliliters of iohexol (180 mg/mL) by lumbar intrathecal injection, approximately 88 (73.1-98.2) percent of the injected dose was excreted in the urine within the first 24 hours after administration. The renal and body clearances were 99 (47-137) milliliters per minute and 109 (52-138) milliliters per minute. The mean maximal plasma concentration was 119 (72-177) micrograms of iohexol per milliliter and occurred after 3.8 (2-6) hours. The volume of distribution was 557 (350-849) milliliters per kilogram. In one patient with a large spinal cord tumor, excretion was delayed (67 percent of the dose appeared in the urine within the first 24 hours) with no difference in the total overall recovery in the urine after 48 hours. The delay in excretion appeared to be related to a decrease in the rate of transfer of iohexol from the cerebrospinal fluid to the blood (plasma maximal concentration was approximately 30 micrograms/mL).

The initial concentration and volume of the medium, in conjunction with appropriate patient manipulation and the volume of CSF into which the medium is placed, will determine the extent of the diagnostic contrast that can be achieved.

Following intrathecal injection in conventional radiography, OMNIPAQUE 180, OMNIPAQUE 240, and OMNIPAQUE 300 will continue to provide good diagnostic contrast for at least 30 minutes. Slow diffusion of iohexol takes place throughout the CSF with subsequent absorption into the bloodstream. Once in the systemic circulation, iohexol displays little tendency to bind to serum or plasma proteins. At approximately 1 hour following injection, contrast of diagnostic quality will no longer be available for conventional myelography. If computerized tomographic (CT) myelography is to follow, consideration should be given to a delay of several hours to allow the degree of contrast to decrease.

After administration into the lumbar subarachnoid space, computerized tomography shows the presence of contrast medium in the thoracic region in about 1 hour, in the cervical region in about 2 hours, and in the basal cisterns in 3 to 4 hours.

In patients with renal impairment, depending on the degree of impairment, prolonged plasma iohexol levels may be anticipated due to decreased renal elimination.

INDICATIONS AND USAGE—Intrathecal

OMNIPAQUE 180, OMNIPAQUE 240, and OMNIPAQUE 300 are indicated for intrathecal administration in adults including myelography (lumbar, thoracic, cervical, total columnar) and in contrast enhancement for computerized tomography (myelography, cisternography, ventriculography).

OMNIPAQUE 180 is indicated for intrathecal administration in children including myelography (lumbar, thoracic, cervical, total columnar) and in contrast enhancement for computerized tomography (myelography, cisternography).

CONTRAINDICATIONS—Intrathecal

OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

Myelography should not be performed in the presence of significant local or systemic infection where bacteremia is likely.

Intrathecal administration of corticosteroids with OMNIPAQUE is contraindicated.

Because of the possibility of overdosage, immediate repeat myelography in the event of technical failure is contraindicated (see DOSAGE AND ADMINISTRATION).

WARNINGS—General

SEVERE ADVERSE EVENTS—INADVERTENT INTRATHECAL ADMINISTRATION

Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that OMNIPAQUE 140 and 350 are not administered intrathecally. (All other concentrations of OMNIPAQUE are approved for intrathecal administration.)

If grossly bloody CSF is encountered, the possible benefits of a myelographic procedure should be considered in terms of the risk to the patient.

Caution is advised in patients with a history of epilepsy, severe cardiovascular disease, chronic alcoholism, or multiple sclerosis.

Elderly patients may present a greater risk following myelography. The need for the procedure in these patients should be evaluated carefully. Special attention must be paid to dose and concentration of the medium, hydration, and technique used.

Patients who are receiving anticonvulsants should be maintained on this therapy. Should a seizure occur, intravenous diazepam or phenobarbital sodium is recommended. In patients with a history of seizure activity who are not on anticonvulsant therapy, premedication with barbiturates should be considered.

Prophylactic anticonvulsant treatment with barbiturates should be considered in patients with evidence of inadvertent intracranial entry of a large or concentrated bolus of the contrast medium since there may be an increased risk of seizure in such cases.

Drugs which lower the seizure threshold, especially phenothiazine derivatives, including those used for their antihistamine properties, are not recommended for use with OMNIPAQUE. Others include MAO inhibitors, tricyclic antidepressants, CNS stimulants, and psychoactive drugs described as analeptics, major tranquilizers, or antipsychotic drugs. While the contributory role of these medications has not been established, the use of such drugs should be based on physician evaluation of potential benefits and potential risks. Physicians have discontinued these agents at least 48 hours before and for at least 24 hours postprocedure.

Care is required in patient management to prevent inadvertent intracranial entry of a large dose or concentrated bolus of the medium. Also, effort should be directed to avoid rapid dispersion of the medium causing inadvertent rise to intracranial levels (eg, by active patient movement). Direct intracisternal or ventricular administration for standard radiography (not CT) is not recommended.

In most reported cases of major motor seizures with nonionic myelographic media, one or more of the following factors were present. Therefore avoid:

- Deviations from recommended procedure or in myelographic management.
- Use in patients with a history of epilepsy.
- Overdosage.
- Intracranial entry of a bolus or premature diffusion of a high concentration of the medium.
- Medication with neuroleptic drugs or phenothiazine antiemetics.
- Failure to maintain elevation of the head during the procedure, on the stretcher, or in bed.
- Excessive and particularly active patient movement or straining.

PRECAUTIONS—General

Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions have occurred. (See ADVERSE REACTIONS.)

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease). Dehydration in these patients seems to be enhanced by the osmotic diuretic action of contrast agents. *Patients should be well hydrated prior to and following administration of any contrast medium, including iohexol.*

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid, cardiovascular or central nervous system reactions, should always be considered (see ADVERSE REACTIONS). Therefore, it is of utmost importance that a course of action be carefully planned in advance for the immediate treatment of serious reactions, and that adequate and appropriate facilities and personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. Recent reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

In patients with severe renal insufficiency or failure, compensatory biliary excretion of the drug is anticipated to occur, with a slow clearance into the bile. Patients with hepatorenal insufficiency should not be examined unless the possibility of benefit clearly outweighs the additional risk.

Administration of contrast media should be performed by qualified personnel familiar with the procedure and appropriate patient management (see PATIENT MANAGEMENT). Sterile technique must be used with any spinal puncture.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal

clearance of the drug from the body (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

Information for Patients (or if applicable, children)

Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant (see CLINICAL PHARMACOLOGY).
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease or known thyroid disorder (see WARNINGS).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS—General).
4. Inform your physician about any other medications you are currently taking, including non-prescription drugs, before you are administered this drug.

Drug Interactions

Drugs which lower seizure threshold, especially phenothiazine derivatives including those used for their antihistaminic or antinauseant properties, are not recommended for use with OMNIPAQUE. Others include monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, CNS stimulants, psychoactive drugs described as analeptics, major tranquilizers, or antipsychotic drugs. Such medications should be discontinued at least 48 hours before myelography, should not be used for the control of nausea or vomiting during or after myelography, and should not be resumed for at least 24 hours postprocedure. In nonelective procedures in patients on these drugs, consider prophylactic use of anticonvulsants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

ADVERSE REACTIONS—Intrathecal

The most frequently reported adverse reactions with OMNIPAQUE are headache, mild to moderate pain including backache, neckache and stiffness, nausea, and vomiting. These reactions usually occur 1 to 10 hours after injection, and almost all occur within 24 hours. They are usually mild to moderate in degree, lasting for a few hours, and usually disappearing within 24 hours. Rarely, headaches may be severe or persist for days. Headache is often accompanied by nausea and vomiting and tends to be more frequent and persistent in patients not optimally hydrated.

Transient alterations in vital signs may occur and their significance must be assessed on an individual basis. Those reactions reported in clinical studies with OMNIPAQUE are listed below in decreasing order of occurrence, based on clinical studies of 1531 patients.

Headaches: The most frequently occurring adverse reaction following myelography has been headache, with an incidence of approximately 18%. Headache may be caused by either a direct effect of the contrast medium or by CSF leakage at the dural puncture site. However, in managing the patient, it is considered more important to minimize intracranial entry of contrast medium by postural management than attempting to control possible CSF leakage (see PATIENT MANAGEMENT).

Pain: Mild to moderate pain including backache, neckache and stiffness, and neuralgia occurred following injection with an incidence of about 8%.

Nausea and Vomiting: Nausea was reported with an incidence of about 6%, and vomiting about 3% (see PATIENT MANAGEMENT). Maintaining normal hydration is very important. The use of phenothiazine antinauseants is not recommended. (See WARNINGS—General.) Reassurance to the patient that the nausea will clear usually is all that is required.

Dizziness: Transient dizziness was reported in about 2% of the patients.

Other Reactions: Other reactions occurring with an individual incidence of less than 0.1% included: feeling of heaviness, hypotension, hypertonia, sensation of heat, sweating, vertigo, loss of appetite, drowsiness, hypertension, photophobia, tinnitus, neuralgia, paresthesia, difficulty in micturition, and neurological changes. All were transient and mild with no clinical sequelae.

Pediatrics

In controlled clinical trials involving 152 patients for pediatric myelography by lumbar puncture, adverse events following the use of OMNIPAQUE 180 were generally less frequent than with adults.

Headache: 9%

Vomiting: 6%

Backache: 1.3%

Other Reactions: Other reactions occurring with an individual incidence of less than 0.7% included: fever, hives, stomachache, visual hallucination, and neurological changes. All were transient and mild with no clinical sequelae.

General Adverse Reactions to Contrast Media

Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above, particularly the following reactions which have been reported in the literature for other nonionic, water-soluble myelographic media, and rarely with iohexol. These have included, but are not limited to, convulsion, aseptic and bacterial meningitis, and CNS and other neurological disturbances.

An aseptic meningitis syndrome has been reported rarely (less than 0.01%). It was usually preceded by pronounced headaches, nausea and vomiting. Onset usually occurred about 12 to 18 hours postprocedure. Prominent features were meningismus, fever, sometimes with oculomotor signs and mental confusion. Lumbar puncture revealed a high white cell count, high protein content often with a low glucose level and with absence of organisms. The condition usually started to clear spontaneously about 10 hours after onset, with complete recovery over 2 to 3 days.

Allergy or Idiosyncrasy: Chills, fever, profuse diaphoresis, pruritus, urticaria, nasal congestion, dyspnea, and a case of Guillain-Barre syndrome.

CNS Irritation: Mild and transitory perceptual aberrations such as hallucinations, depersonalization, amnesia, hostility, amblyopia, diplopia, photophobia, psychosis, insomnia, anxiety, depression, hyperesthesia, visual or auditory or speech disturbances, confusion and disorientation. In addition, malaise, weakness, convulsion, EEG changes, meningismus, hyperreflexia or areflexia, hypertonia or flaccidity, hemiplegia, paralysis, quadriplegia, restlessness, tremor, echoacousia, echolalia, asterixis, cerebral hemorrhage, and dysphasia have occurred.

Profound mental disturbances have also rarely been reported. They have usually consisted of various forms and degrees of aphasia, mental confusion, or disorientation. The onset is usually at 8 to 10 hours and lasts for about 24 hours, without aftereffects. However, occasionally they have been manifest as apprehension, agitation, or progressive withdrawal in several instances to the point of somnolence, stupor, and coma. In a few cases these have been accompanied by transitory hearing loss or other auditory symptoms and visual disturbances (believed subjective or delusional), including unilateral or bilateral loss of vision which may last for hours. In one case, persistent cortical loss of vision has been reported in association with convulsions. Ventricular block has been reported; amnesia of varying degrees may be present for the reaction event.

Rarely, persistent though transitory weakness in the leg or ocular muscles has been reported.

Peripheral neuropathies have been rare and transitory. They include sensory and/or motor or nerve root disturbances, myelitis, persistent leg muscle pain or weakness, 6th nerve palsy, or cauda equina syndrome. Muscle cramps, fasciculation or myoclonia, spinal convulsion, or spasticity is unusual and has responded promptly to a small intravenous dose of diazepam.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95 percent of adverse reactions accompanying the use of water-soluble contrast agents are mild to moderate in degree. However, severe, life-threatening, anaphylactoid and fatal reactions, mostly of cardiovascular origin and central nervous system origin, have occurred.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

OVERDOSAGE

Clinical consequences of overdosage with OMNIPAQUE have not been reported. However, based on experience with other nonionic myelographic media, physicians should be alert to a potential increase in frequency and severity of CNS-mediated reactions. Even use of a recommended dose can produce effects tantamount to overdosage, if incorrect management of the patient during or immediately following the procedure permits inadvertent early intracranial entry of a large portion of the medium. The intracisternal LD₅₀ value of OMNIPAQUE (in grams of iodine per kilogram body weight) is greater than 2.0 in mice.

DOSAGE AND ADMINISTRATION – Intrathecal

The volume and concentration of OMNIPAQUE 180, OMNIPAQUE 240, or OMNIPAQUE 300 to be administered will depend on the degree and extent of contrast required in the area(s) under examination and on the equipment and technique employed.

OMNIPAQUE 180 at a concentration of 180 mgI/mL, OMNIPAQUE 240 at a concentration of 240 mgI/mL, or OMNIPAQUE 300 at a concentration of 300 mgI/mL is recommended for the examination of the lumbar, thoracic, and cervical regions in adults by lumbar or direct cervical injection and is slightly hypertonic to CSF.

OMNIPAQUE 180 at a concentration of 180 mgI/mL is recommended for the examination of the lumbar, thoracic, and cervical regions in children by lumbar injection and is slightly hypertonic to CSF.

A total dose of 3060 mg iodine or a concentration of 300 mgI/mL should not be exceeded in adults and a total dose of 2700 mg iodine or a concentration of 180 mgI/mL should not be exceeded in children in a single myelographic examination. This is based on clinical trial evaluation to date. As in all diagnostic procedures, the minimum volume and dose to produce adequate visualization should be used. Most procedures do not require either maximum dose or concentration.

Anesthesia is not necessary. Premedication sedatives or tranquilizers are usually not needed (see PRECAUTIONS). Patients should be well hydrated prior to and following contrast administration. Seizure-prone patients should be maintained on anticonvulsant medication.

Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs; therefore, concurrent drugs should not be physically admixed with contrast agents.

Rate of Injection: To avoid excessive mixing with CSF and consequent dilution of contrast, injection should be made slowly over 1 to 2 minutes.

Depending on the estimated volume of contrast medium which may be required for the procedure a small amount of CSF may be removed to minimize distention of the subarachnoid spaces.

The lumbar or cervical puncture needle may be removed immediately following injection since it is not necessary to remove OMNIPAQUE after injection into the subarachnoid space.

Adults: The usual recommended total doses for use in lumbar, thoracic, cervical, and total columnar myelography in adults are 1.2 gI to 3.06 gI as follows:

Procedure	Formulations	Concentration (mgI/mL)	Volume (mL)	Dose (gI)
Lumbar Myelography (via lumbar injection)	OMNIPAQUE 180 OMNIPAQUE 240	180 240	10-17 7-12.5	1.8-3.06 1.7-3.0
Thoracic Myelography (via lumbar or cervical injection)	OMNIPAQUE 240 OMNIPAQUE 300	240 300	6-12.5 6-10	1.7-3.0 1.8-3.0
Cervical Myelography (via lumbar injection)	OMNIPAQUE 240 OMNIPAQUE 300	240 300	6-12.5 6-10	1.4-3.0 1.8-3.0
Cervical Myelography (via C1-2 injection)	OMNIPAQUE 180 OMNIPAQUE 240 OMNIPAQUE 300	180 240 300	7-10 6-12.5 4-10	1.3-1.8 1.4-3.0 1.2-3.0
Total Columnar Myelography (via lumbar injection)	OMNIPAQUE 240 OMNIPAQUE 300	240 300	6-12.5 6-10	1.4-3.0 1.8-3.0

Pediatrics: The usual recommended total doses for lumbar, thoracic, cervical, and/or total columnar myelography by lumbar puncture in children are 0.36 gI to 2.7 gI (see table below). Actual volumes administered depend largely on patient age and the following guidelines are recommended.

Age	Conc. (mgI/mL)	Volume (mL)	Dose (gI)
0 to < 3 mos.	180	2-4	0.36-0.72
3 to < 36 mos.	180	4-8	0.72-1.44
3 to < 7 yrs.	180	5-10	0.9-1.8
7 to < 13 yrs.	180	5-12	0.9-2.16
13 to 18 yrs.	180	6-15	1.08-2.7

Withdrawal of contrast agents from their containers should be accomplished under aseptic conditions with sterile syringes. Spinal puncture must always be performed under sterile conditions.

Parenteral products should be inspected visually for particulate matter or discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal

clearance of the drug from the body. An interval of at least 48 hours should be allowed before repeat examination; however, whenever possible, 5 to 7 days is recommended.

PATIENT MANAGEMENT—Intrathecal

Suggestions for Usual Patient Management

Good patient management should be exercised at all times to minimize the potential for procedurally related complications.

Preprocedure

- Discontinuance of neuroleptic drugs (including phenothiazines, eg, chlorpromazine, prochlorperazine, and promethazine) at least 48 hours beforehand should be considered.
- Maintain normal diet up to 2 hours before procedure.
- Ensure hydration-fluids up to procedure.

During Procedure

- Use minimum dose and concentration required for satisfactory contrast (see DOSAGE AND ADMINISTRATION).
- In all positioning techniques keep the patient's head elevated above highest level of spine.
- Do not lower head of table more than 15° in moving contrast medium cranially.
- In patients with excessive lordosis, consider lateral position for injection and movement of the medium cephalad.
- Inject slowly (over 1 to 2 minutes) to avoid excessive mixing.
- To maintain as a bolus, move medium to distal area very slowly. Use fluoroscopic monitoring.
- Avoid intracranial entry of a bolus.
- Avoid early and high cephalad dispersion of the medium.
- Avoid abrupt or active patient movement to minimize excessive mixing of medium with CSF. Instruct patient to remain passive. Move patient slowly and only as necessary.

Postprocedure

- Raise head of stretcher to at least 30° before moving patient onto it.
- Movement onto and off the stretcher should be done slowly with the patient completely passive, maintaining head-up position.
- Before moving patient onto bed, raise head of bed 30° to 45°.
- Advise patient to remain still in bed, in a sitting or semisitting position, especially in the first few hours.
- Maintain close observation for at least 12 hours after myelogram.
- Obtain visitors' cooperation in keeping the patient quiet and in head-up position, especially in first few hours.
- Encourage oral fluids. Diet as tolerated.
- If nausea or vomiting occurs, do not use phenothiazine antiemetics. Persistent nausea and vomiting will result in dehydration. Therefore, prompt consideration of replacement by intravenous fluids is recommended.

Alternative Postprocedure Method

- Recent evidence with nonionic, water-soluble contrast media suggests that maintaining the patient postmyelography in an upright position (via wheelchair or ambulation) may help minimize adverse effects. The upright position may help to delay upward dispersion of the medium and to maximize the spinal arachnoid absorption.

HOW SUPPLIED

OMNIPAQUE 180

10 mL glass vial, 180 mgI/mL, boxes of 10 (NDC 0407-1411-10)

20 mL glass vial, 180 mgI/mL, boxes of 10 (NDC 0407-1411-20)

OMNIPAQUE 240

10 mL glass vial, 240 mgI/mL, boxes of 10 (NDC 0407-1412-10)

20 mL glass vial, 240 mgI/mL, boxes of 10 (NDC 0407-1412-20)

OMNIPAQUE 300

10 mL glass vial, 300 mgI/mL, boxes of 10 (NDC 0407-1413-10)

Storage: Protect vials of OMNIPAQUE from strong daylight and direct exposure to sunlight. Do not freeze. OMNIPAQUE should be stored at controlled room temperature, 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

SECTION II

CLINICAL PHARMACOLOGY—Intravascular

Following intravascular injection, iohexol is distributed in the extracellular fluid compartment and is excreted unchanged by glomerular filtration. It will opacify those vessels in the path of flow of the contrast medium permitting radiographic visualization of the internal structures until significant hemodilution occurs.

Approximately 90% or more of the injected dose is excreted within the first 24 hours, with the peak urine concentrations occurring in the first hour after administration. Plasma and urine iohexol levels

indicate that the iohexol body clearance is due primarily to renal clearance. An increase in the dose from 500 mgI/kg to 1500 mgI/kg does not significantly alter the clearance of the drug. The following pharmacokinetic values were observed following the intravenous administration of iohexol (between 500 mgI/kg to 1500 mgI/kg) to 16 adult human subjects: renal clearance—120 (86-162) mL/min; total body clearance—131 (98-165) mL/min; and volume of distribution—165 (108-219) mL/kg.

Renal accumulation is sufficiently rapid that the period of maximal opacification of the renal passages may begin as early as 1 minute after intravenous injection. Urograms become apparent in about 1 to 3 minutes with optimal contrast occurring between 5 to 15 minutes. In nephropathic conditions, particularly when excretory capacity has been altered, the rate of excretion may vary unpredictably, and opacification may be delayed after injection. Severe renal impairment may result in a lack of diagnostic opacification of the collecting system and, depending on the degree of renal impairment, prolonged plasma iohexol levels may be anticipated. In these patients, as well as in infants with immature kidneys, the route of excretion through the gallbladder and into the small intestine may increase.

Iohexol displays a low affinity for serum or plasma proteins and is poorly bound to serum albumin. No significant metabolism, deiodination or biotransformation occurs.

OMNIPAQUE probably crosses the placental barrier in humans by simple diffusion. It is not known to what extent iohexol is excreted in human milk.

Animal studies indicate that iohexol does not cross an intact blood-brain barrier to any significant extent following intravascular administration.

OMNIPAQUE enhances computed tomographic imaging through augmentation of radiographic efficiency. The degree of density enhancement is directly related to the iodine content in an administered dose; peak iodine blood levels occur immediately following rapid intravenous injection. Blood levels fall rapidly within 5 to 10 minutes and the vascular compartment half-life is approximately 20 minutes. This can be accounted for by the dilution in the vascular and extravascular fluid compartments which causes an initial sharp fall in plasma concentration. Equilibration with the extracellular compartments is reached in about ten minutes; thereafter, the fall becomes exponential.

The pharmacokinetics of iohexol in both normal and abnormal tissue have been shown to be variable. Contrast enhancement appears to be greatest immediately after bolus administration (15 seconds to 120 seconds). Thus, greatest enhancement may be detected by a series of consecutive two-to-three second scans performed within 30 to 90 seconds after injection (ie, dynamic computed tomographic imaging). Utilization of a continuous scanning technique (ie, dynamic CT scanning) may improve enhancement and diagnostic assessment of tumor and other lesions such as abscess, occasionally revealing unsuspected or more extensive disease. For example, a cyst may be distinguished from a vascularized solid lesion when precontrast and enhanced scans are compared; the nonperfused mass shows unchanged x-ray absorption (CT number). A vascularized lesion is characterized by an increase in CT number in the few minutes after a bolus of intravascular contrast agent; it may be malignant, benign, or normal tissue, but would probably not be a cyst, hematoma, or other nonvascular lesion.

Because unenhanced scanning may provide adequate diagnostic information in the individual patient, the decision to employ contrast enhancement, which may be associated with risk and increased radiation exposure, should be based upon a careful evaluation of clinical, other radiological, and unenhanced CT findings.

CT SCANNING OF THE HEAD

In contrast enhanced computed tomographic head imaging, OMNIPAQUE does not accumulate in normal brain tissue due to the presence of the normal blood-brain barrier. The increase in x-ray absorption in normal brain is due to the presence of contrast agent within the blood pool. A break in the blood-brain barrier such as occurs in malignant tumors of the brain allows for the accumulation of contrast medium within the interstitial tissue of the tumor. Adjacent normal brain tissue does not contain the contrast medium.

Maximum contrast enhancement in tissue frequently occurs after peak blood iodine levels are reached. A delay in maximum contrast enhancement can occur. Diagnostic contrast enhanced images of the brain have been obtained up to 1 hour after intravenous bolus administration. This delay suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine containing medium within the lesion and outside the blood pool, although the mechanism by which this occurs is not clear. The radiographic enhancement of nontumoral lesions, such as arteriovenous malformations and aneurysms, is probably dependent on the iodine content of the circulating blood pool.

In patients where the blood-brain barrier is known or suspected to be disrupted, the use of any radiographic contrast medium must be assessed on an individual risk to benefit basis. However, compared to ionic media, nonionic media are less toxic to the central nervous system.

CT SCANNING OF THE BODY

In contrast enhanced computed tomographic body imaging (nonneural tissue), OMNIPAQUE diffuses rapidly from the vascular into the extravascular space. Increase in x-ray absorption is related to blood flow, concentration of the contrast medium, and extraction of the contrast medium by interstitial tissue of tumors since no barrier exists. Contrast enhancement is thus due to the relative differences in extravascular diffusion between normal and abnormal tissue, quite different from that in the brain.

INDICATIONS AND USAGE, GENERAL—Intravascular

OMNIPAQUE 350 is indicated in adults for angiocardiology (ventriculography, selective coronary arteriography), aortography including studies of the aortic root, aortic arch, ascending aorta, abdominal aorta and its branches, contrast enhancement for computed tomographic head and body

imaging, intravenous digital subtraction angiography of the head, neck, abdominal, renal and peripheral vessels, peripheral arteriography, and excretory urography.

OMNIPAQUE 350 is indicated in children for angiocardiology (ventriculography, pulmonary arteriography, and venography; studies of the collateral arteries and aortography, including the aortic root, aortic arch, ascending and descending aorta).

OMNIPAQUE 300 is indicated in adults for aortography including studies of the aortic arch, abdominal aorta and its branches, contrast enhancement for computed tomographic head and body imaging, cerebral arteriography, peripheral venography (phlebography), and excretory urography.

OMNIPAQUE 300 is indicated in children for angiocardiology (ventriculography), excretory urography, and contrast enhancement for computed tomographic head imaging.

OMNIPAQUE 240 is indicated in adults for contrast enhancement for computed tomographic head imaging and peripheral venography (phlebography).

OMNIPAQUE 140 is indicated in adults for intra-arterial digital subtraction angiography of the head, neck, abdominal, renal and peripheral vessels.

OMNIPAQUE 240 is indicated in children for contrast enhancement for computed tomographic head imaging.

CONTRAINDICATIONS

OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS—General

Nonionic iodinated contrast media inhibit blood coagulation, *in vitro*, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

OMNIPAQUE should be used with extreme care in patients with severe functional disturbances of the liver and kidneys, severe thyrotoxicosis, or myelomatosis. Diabetics with a serum creatinine level above 3 mg/dL should not be examined unless the possible benefits of the examination clearly outweigh the additional risk. OMNIPAQUE is not recommended for use in patients with anuria.

Radiopaque contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Although neither the contrast agent nor dehydration has separately proven to be the cause of anuria in myeloma, it has been speculated that the combination of both may be causative factors. The risk in myelomatous patients is not a contraindication; however, special precautions are necessary. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before instituting intravascular administration of contrast agents.

Ionic contrast media, when injected intravenously or intra-arterially, may promote sickling in individuals who are homozygous for sickle cell disease.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The patient's blood pressure should be assessed throughout the procedure and measures for the treatment of hypertensive crisis should be readily available.

Reports of thyroid storm following the use of iodinated, ionic radiopaque contrast media in patients with hyperthyroidism or with an autonomously functioning thyroid nodule suggest that this additional risk be evaluated in such patients before use of any contrast medium.

Urography should be performed with caution in patients with severely impaired renal function and patients with combined renal and hepatic disease.

PRECAUTIONS—General

Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions have occurred (see ADVERSE REACTIONS: Intravascular—General).

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease), infants and small children. Dehydration in these patients seems to be enhanced by the osmotic diuretic action of urographic agents. It is believed that overnight fluid

restriction prior to excretory urography generally does not provide better visualization in normal patients. *Patients should be well hydrated prior to and following administration of any contrast medium, including iohexol.*

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible non-diabetic patients (often elderly with preexisting renal disease) following excretory urography. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Immediately following surgery, excretory urography should be used with caution in renal transplant recipients.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (see ADVERSE REACTIONS: Intravascular—General). It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate and appropriate personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS: Intravascular—General). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS: Intravascular—General). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered and administered using separate syringes. Recent reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

Even though the osmolality of OMNIPAQUE is low compared to diatrizoate- or iohalamate-based ionic agents of comparable iodine concentration, the potential transitory increase in the circulatory osmotic load in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

General anesthesia may be indicated in the performance of some procedures in selected adult patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms, or to the hypotensive effect of anesthesia which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be borne in mind during the catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the potential risk. The inherent risks of angiocardiology in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Information for Patients

Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant (see CLINICAL PHARMACOLOGY—Intravascular).
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see WARNINGS).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS—General).
4. Inform your physician about any other medications you are currently taking, including non-prescription drugs, before you are administered this drug.

Drug/Laboratory Test Interaction

If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, eg, T_3 resin uptake or direct thyroxine assays, are not affected.

Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

ADVERSE REACTIONS: Intravascular—General

Adverse reactions following the use of OMNIPAQUE 140, OMNIPAQUE 240, OMNIPAQUE 300, and OMNIPAQUE 350 are usually of mild to moderate severity. However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media, including OMNIPAQUE. The injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral angiography; pain and warmth are less frequent and less severe with OMNIPAQUE than with many contrast media.

Cardiovascular System: Arrhythmias including PVCs and PACs (2%), angina/chest pain (1%), and hypotension (0.7%). Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported with an individual incidence of 0.3% or less. In controlled clinical trials involving 1485 patients, one fatality occurred. A cause and effect relationship between this death and iohexol has not been established.

Nervous System: Vertigo (including dizziness and lightheadedness) (0.5%), pain (3%), vision abnormalities (including blurred vision and photomas) (2%), headache (2%), and taste perversion (1%). Others including anxiety, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus were reported, with an individual incidence of 0.3% or less.

Respiratory System: Dyspnea, rhinitis, coughing, and laryngitis, with an individual incidence of 0.2% or less.

Gastrointestinal System: Nausea (2%) and vomiting (0.7%). Others including diarrhea, dyspepsia, cramp, and dry mouth were reported, with an individual incidence of less than 0.1%.

Skin and Appendages: Urticaria (0.3%), purpura (0.1%), abscess (0.1%), and pruritus (0.1%).

Individual adverse reactions which occurred to a significantly greater extent for a specific procedure are listed under that indication.

Pediatrics

In controlled clinical trials involving 391 patients for pediatric angiocardiology, urography, and contrast enhanced computed tomographic head imaging, adverse reactions following the use of OMNIPAQUE 240, OMNIPAQUE 300, and OMNIPAQUE 350 were generally less frequent than with adults.

Cardiovascular System: Ventricular tachycardia (0.5%), 2:1 heart block (0.5%), hypertension (0.3%), and anemia (0.3%).

Nervous System: Pain (0.8%), fever (0.5%), taste abnormality (0.5%), and convulsion (0.3%).

Respiratory System: Congestion (0.3%) and apnea (0.3%).

Gastrointestinal System: Nausea (1%), hypoglycemia (0.3%), and vomiting (2%).

Skin and Appendages: Rash (0.3%).

General Adverse Reactions to Contrast Media

Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above.

The following reactions have been reported after administration of other intravascular iodinated contrast media, and rarely with iohexol. **Reactions due to technique:** hematomas and ecchymoses. **Hemodynamic reactions:** vein cramp and thrombophlebitis following intravenous injection. **Cardiovascular reactions:** rare cases of cardiac arrhythmias, reflex tachycardia, chest pain, cyanosis, hypertension, hypotension, peripheral vasodilatation, shock, and cardiac arrest. **Renal reactions:** occasionally, transient proteinuria, and rarely, oliguria or anuria. **Allergic reactions:** asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria with or without pruritus, as well as pleomorphic rashes, sneezing and lacrimation and, rarely, anaphylactic reactions. Rare fatalities have occurred, due to this or unknown causes. **Signs and symptoms related to the respiratory system:** pulmonary or laryngeal edema, bronchospasm, dyspnea; or to the nervous system: restlessness, tremors, convulsions. **Other reactions:** flushing, pain, warmth, metallic taste, nausea, vomiting, anxiety, headache, confusion, pallor, weakness, sweating, localized areas of edema, especially facial cramps, neutropenia, and dizziness. Rarely, immediate or delayed rigors can occur, sometimes accompanied by

hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears two days after exposure and subsides by the sixth day.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95 percent of adverse reactions accompanying the use of water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred. Reported incidences of death range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 (0.01 percent). Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005 percent) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy are twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with angiocardiology than with other procedures. Cardiac decompensation, serious arrhythmias, angina pectoris, or myocardial ischemia or infarction may occur during angiocardiology and left ventriculography. Electrocardiographic and hemodynamic abnormalities occur less frequently with OMNIPAQUE than with diatrizoate meglumine and diatrizoate sodium injection.

OVERDOSAGE

Overdosage may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms include: cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

The intravenous LD₅₀ values of OMNIPAQUE (in grams of iodine per kilogram body weight) are 24.2 in mice and 15.0 in rats.

DOSAGE AND ADMINISTRATION — General

As with all radiopaque contrast agents, the lowest dose of OMNIPAQUE necessary to obtain adequate visualization should be used. A lower dose may reduce the possibility of an adverse reaction. Most procedures do not require use of either the maximum volume or the highest concentration of OMNIPAQUE. The combination of volume and concentration of OMNIPAQUE to be used should be carefully individualized accounting for factors such as age, body weight, size of the vessel and the rate of blood flow within the vessel. Other factors such as anticipated pathology, degree and extent of opacification required, structure(s) or area to be examined, disease processes affecting the patient, and equipment and technique to be employed should be considered.

Sterile technique must be used in all vascular injections involving contrast media.

Withdrawal of contrast agents from their containers should be accomplished under aseptic conditions with sterile equipment. Sterile techniques must be used with any invasive procedure.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

It may be desirable that solutions of radiopaque diagnostic agents be used at body temperature when injected.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions of OMNIPAQUE should be used only if clear and within the normal colorless to pale yellow range. If particulate matter or discoloration is present, do not use.

INDIVIDUAL INDICATIONS AND USAGE

ANGIOCARDIOGRAPHY

Pharmacology—Hemodynamic Changes

OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in adults for angiocardiology (ventriculography, aortic root injections, and selective coronary arteriography).

OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in children for angiocardiology (ventriculography, pulmonary arteriography, and venography, and studies of the collateral arteries).

OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in children for angiocardiology (ventriculography).

After both ventricular and coronary injection, decreases in systolic pressure were less pronounced and returned to baseline values earlier with OMNIPAQUE 350 than with diatrizoate meglumine and diatrizoate sodium injection.

OMNIPAQUE 350 produced less Q-T interval prolongation than seen with diatrizoate meglumine and diatrizoate sodium injection.

In children, after injection of all sites, but particularly following ventricular and pulmonary artery injections, decreases in both systolic and diastolic intravascular pressure were significantly less pronounced with OMNIPAQUE 350 than with diatrizoate meglumine and diatrizoate sodium injection. In children, OMNIPAQUE 350 produced significantly less shortening of the R-R interval than seen with diatrizoate meglumine and diatrizoate sodium injection.

If repeat injections are made in rapid succession, all these changes are likely to be more pronounced. (See DOSAGE AND ADMINISTRATION.)

Precautions

During administration of large doses of OMNIPAQUE 350, continuous monitoring of vital signs is desirable. Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the preexisting condition. Hypotension should be corrected promptly since it may induce serious arrhythmias.

Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds because of the hemodynamic changes which may occur after injection into the right heart outflow tract. (See PRECAUTIONS—General.)

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

Adverse Reactions

Cardiovascular system reactions in angiocardiology included angina (8%), hypotension (2.5%), bradycardia (1.0%), and tachycardia (1.0%). (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The individual dose or volume is determined by the size of the structure to be visualized, the anticipated degree of hemodilution, and valvular competence. Weight is a minor consideration in adults, but must be considered in infants and young children. The volume of each individual injection is a more important consideration than the total dosage used. When large individual volumes are administered, as in ventriculography and aortography, it has been suggested that several minutes be permitted to elapse between each injection to allow for subsidence of possible hemodynamic disturbances.

The recommended single injection volume of OMNIPAQUE 350 for angiocardiology procedures in adults and the recommended single injection volumes of OMNIPAQUE 350 and OMNIPAQUE 300 for angiographic procedures in children are as follows:

Ventriculography

Adults: The usual adult volume for a single injection is 40 mL with a range of 30 mL to 60 mL. This may be repeated as necessary. When combined with selective coronary arteriography, the total administered volume should not exceed 250 mL (87.5 gI).

Pediatrics: The usual single injection dose of OMNIPAQUE 350 is 1.25 mL/kg of body weight with a range of 1.0 mL/kg to 1.5 mL/kg. For OMNIPAQUE 300 the usual single injection dose is 1.75 mL/kg with a range of 1.5 mL/kg to 2.0 mL/kg. When multiple injections are given, the total administered dose should not exceed 5 mL/kg up to a total volume of 250 mL of OMNIPAQUE 350 or up to a total volume of 291 mL of OMNIPAQUE 300.

Selective Coronary Arteriography

The usual adult volume for right or left coronary arteriography is 5 mL (range 3 mL to 14 mL) per injection.

Aortic Root and Arch Study When Used Alone

The usual adult single injection volume is 50 mL, with a range of 20 mL to 75 mL.

Pulmonary Angiography

Pediatrics: The usual single injection dose is 1.0 mL/kg of OMNIPAQUE 350.

Combined Angiocardiology Procedures

Multiple Procedures

Adults: The visualization of multiple vascular systems and target organs is possible during a single radiographic examination of the patient.

Large doses of OMNIPAQUE 350 were well tolerated in angiographic procedures requiring multiple injections.

The maximum total volume for multiple procedures should not exceed 250 mL of 350 mgI/mL (87.5 gI).

Pediatrics: Visualization of multiple vascular systems and target organs is possible during a single radiographic examination of the patient.

The maximum total dose for multiple injection procedures should not exceed 5.0 mL/kg up to a total volume of 250 mL of OMNIPAQUE 350 or 6.0 mL/kg up to a total volume of 291 mL of OMNIPAQUE 300.

AORTOGRAPHY AND

SELECTIVE VISCERAL ARTERIOGRAPHY

OMNIPAQUE 300 at a concentration of 300 mgI/mL and OMNIPAQUE 350 at a concentration of 350 mgI/mL are indicated in adults for use in aortography and selective visceral arteriography including

studies of the aortic arch, ascending aorta, and abdominal aorta and its branches (celiac, mesenteric, renal, hepatic and splenic arteries).

OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in children for use in aortography including studies of the aortic root, aortic arch, ascending and descending aorta.

Precautions

Under conditions of slowed aortic circulation there is an increased likelihood for aortography to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aortoiliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressors to increase contrast. In these patients the concentration, volume and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, and an elevated creatinine and urea nitrogen. Rapid and complete return of function usually follows. (See PRECAUTIONS—General.)

Adverse Reactions

See ADVERSE REACTIONS: Intravascular—General, and ADVERSE REACTIONS—ANGIOCARDIOGRAPHY.

Dosage and Administration

Adults: The usual adult volume as a single injection is 50 mL to 80 mL for the aorta, 30 mL to 60 mL for major branches including celiac and mesenteric arteries, and 5 mL to 15 mL for renal arteries. Repeated injections may be performed if indicated, but the total volume should not exceed 291 mL of OMNIPAQUE 300 or 250 mL of OMNIPAQUE 350 (87.5 gI).

Pediatrics: The usual single injection dose is 1.0 mL/kg of OMNIPAQUE 350 and should not exceed 5.0 mL/kg up to a total volume of 250 mL of OMNIPAQUE 350.

CEREBRAL ARTERIOGRAPHY

OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in adults for use in cerebral arteriography.

The degree of pain and flushing as the result of the use of OMNIPAQUE 300 in cerebral arteriography is less than that seen with comparable injections of many contrast media.

In cerebral arteriography, patients should be appropriately prepared consistent with existing or suspected disease states.

Precautions

Cerebral arteriography should be undertaken with extreme care with special caution in elderly patients, patients in poor clinical condition, advanced arteriosclerosis, severe arterial hypertension, recent cerebral embolism or thrombosis, and cardiac decompensation.

Since the contrast medium is given by rapid injection, the patient should be monitored for possible untoward reactions. (See PRECAUTIONS—General.)

Adverse Reactions

Cerebral arteriography with water-soluble contrast media has been associated with temporary neurologic complications including seizures, drowsiness, transient paresis, and mild disturbances in vision such as photomas of 1-second or less duration.

Central nervous system reactions in cerebral arteriography included photomas (15%), headache (5.5%), and pain (4.5%). (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

OMNIPAQUE 300 is recommended for cerebral arteriography at the following volumes: common carotid artery (6 mL to 12 mL), internal carotid artery (8 mL to 10 mL), external carotid artery (6 mL to 9 mL), and vertebral artery (6 mL to 10 mL).

CONTRAST ENHANCED COMPUTED TOMOGRAPHY

OMNIPAQUE 240 at a concentration of 240 mgI/mL, OMNIPAQUE 300 at a concentration of 300 mgI/mL, and OMNIPAQUE 350 at a concentration of 350 mgI/mL are indicated in adults for use in intravenous contrast enhanced computed tomographic head and body imaging by rapid injection or infusion technique.

OMNIPAQUE 240 at a concentration of 240 mgI/mL and OMNIPAQUE 300 at a concentration of 300 mgI/mL are indicated in children for use in intravenous contrast enhanced computed tomographic head imaging by rapid bolus injection.

CT SCANNING OF THE HEAD

OMNIPAQUE may be used to redefine diagnostic precision in areas of the brain which may not otherwise have been satisfactorily visualized.

Tumors

OMNIPAQUE may be useful to investigate the presence and extent of certain malignancies such as: gliomas including malignant gliomas, glioblastomas, astrocytomas, oligodendrogliomas and gangliomas, ependymomas, medulloblastomas, meningiomas, neuromas, pinealomas, pituitary adenomas, carniopharyngiomas, germinomas, and metastatic lesions. The usefulness of contrast enhancement for the investigation of the retrobulbar space and in cases of low grade or infiltrative glioma has not been demonstrated. In calcified lesions, there is less likelihood of enhancement. Following therapy, tumors may show decreased or no enhancement. The opacification of the inferior vermis following

contrast media administration has resulted in false-positive diagnosis in a number of otherwise normal studies.

Nonneoplastic Conditions

OMNIPAQUE may be beneficial in the image enhancement of nonneoplastic lesions. Cerebral infarctions of recent onset may be better visualized with contrast enhancement, while some infarctions are obscured if contrast medium is used. The use of iodinated contrast media results in enhancement in about 60 percent of cerebral infarctions studied from one to four weeks from the onset of symptoms.

Sites of active infection may also be enhanced following contrast medium administration.

Arteriovenous malformations and aneurysms will show contrast enhancement. For these vascular lesions the enhancement is probably dependent on the iodine content of the circulating blood pool. Hematomas and intraparenchymal bleeders seldom demonstrate contrast enhancement. However, in cases of intraparenchymal clot, for which there is no obvious clinical explanation, contrast media administration may be helpful in ruling out the possibility of associated arteriovenous malformation.

CT SCANNING OF THE BODY

OMNIPAQUE may be useful for enhancement of computed tomographic images for detection and evaluation of lesions in the liver, pancreas, kidneys, aorta, mediastinum, pelvis, abdominal cavity, and retroperitoneal space.

Enhancement of computed tomography with OMNIPAQUE may be of benefit in establishing diagnoses of certain lesions in these sites with greater assurance than is possible with CT alone. In other cases, the contrast agent may allow visualization of lesions not seen with CT alone (ie, tumor extension) or may help to define suspicious lesions seen with unenhanced CT (ie, pancreatic cyst).

For information regarding the use of dilute oral plus intravenous OMNIPAQUE in CT of the abdomen, see INDIVIDUAL INDICATIONS AND USAGE—Oral Use.

Precautions

See PRECAUTIONS—General.

Adverse Reactions

Immediately following intravascular injection of contrast medium, a transient sensation of mild warmth is not unusual. Warmth is less frequent with OMNIPAQUE than with ionic media. (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The concentration and volume required will depend on the equipment and imaging technique used.

OMNIPAQUE (iohexol) Injection

The dosage recommended for use in adults for contrast enhanced computed tomography is as follows:

Head Imaging	70 mL to 150 mL (21 gI to 45 gI) of OMNIPAQUE 300 (300 mgI/mL)
by Injection:	80 mL (28 gI) of OMNIPAQUE 350 (350 mgI/mL)
Head Imaging	120 mL to 250 mL (29 gI to 60 gI) of OMNIPAQUE 240 (240 mgI/mL)
by Infusion:	
Body Imaging	50 mL to 200 mL (15 gI to 60 gI) of OMNIPAQUE 300 (300 mgI/mL)
by Injection:	60 mL to 100 mL (21 gI to 35 gI) of OMNIPAQUE 350 (350 mgI/mL)

The dosage recommended for use in children for contrast enhanced computed tomographic head imaging is 1.0 mL/kg to 2.0 mL/kg for OMNIPAQUE 240 or OMNIPAQUE 300. It should not be necessary to exceed a maximum dose of 28 gI with OMNIPAQUE 240 or 35 gI with OMNIPAQUE 300.

DIGITAL SUBTRACTION ANGIOGRAPHY

Intravenous Administration

OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in adults for use in intravenous digital subtraction angiography (I.V.DSA) of the vessels of the head, neck, and abdominal, renal and peripheral vessels.

Arteriograms of diagnostic quality can be obtained following the intravenous administration of contrast media employing digital subtraction and computer imaging enhancement techniques. The intravenous route of administration using these techniques has the advantage of being less invasive than the corresponding selective catheter placement of medium. The dose is administered into a peripheral vein, the superior vena cava or right atrium, usually by mechanical injection although sometimes by rapid manual injection. The technique has been used to visualize the ventricles, aorta and most of its larger branches, including the carotids, cerebrals, vertebrals, renal, celiac, mesenterics, and the major peripheral vessels of the limbs. Radiographic visualization of these structures is possible until significant hemodilution occurs.

OMNIPAQUE 350 can be injected intravenously as a rapid bolus to provide arterial visualization using digital subtraction radiography. Preprocedural medications are not considered necessary. OMNIPAQUE 350 has provided diagnostic arterial radiographs in about 95% of patients. In some cases, poor arterial visualization has been attributed to patient movement. OMNIPAQUE 350 is very well tolerated in the vascular system. Patient discomfort (general sensation of heat and/or pain) following injection is less than with various other contrast media.

Precautions

Since the contrast medium is usually administered mechanically under high pressure, rupture of smaller peripheral veins can occur. It has been suggested that this can be avoided by using an intravenous catheter threaded proximally beyond larger tributaries or, in the case of the antecubital vein, into the superior vena cava. Sometimes the femoral vein is used. (See PRECAUTIONS—General.)

Adverse Reactions

Cardiovascular system reactions in digital arteriography included transient PVCs (16%) and PACs (6.5%). (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The usual injection volume of OMNIPAQUE 350 for the intravenous digital technique is 30 mL to 50 mL of a 350 mgI/mL solution. This is administered as a bolus at 7.5 to 30 mL/second using a pressure injector. The volume and rate of injection will depend primarily on the type of equipment and technique used.

Frequently three or more injections may be required, up to a total volume not to exceed 250 mL (87.5 gI).

Intra-arterial Administration

OMNIPAQUE 140 at a concentration of 140 mgI/mL is indicated for use in intra-arterial digital subtraction angiography of head, neck, abdominal, renal and peripheral vessels. The intra-arterial route of administration has the advantages of allowing a lower total dose of contrast agent since there is less hemodilution than with the intravenous route of administration. Patients with poor cardiac output would be expected to have better contrast enhancement following intra-arterial administration as compared with intravenous administration. A higher concentration of contrast agent may be needed to facilitate catheter placement under fluoroscopic control.

Precautions

High pressure intra-arterial injections may cause the rupture of smaller peripheral arteries. (See PRECAUTIONS—General.)

Adverse Reactions

Central nervous system reactions in intra-arterial digital angiography include transient ischemia attacks (1.6%) and cerebral infarctions (1.6%). These occurred in high risk patients having a cerebral examination and the relationship to the contrast medium was uncertain. (See ADVERSE REACTIONS—General.) Headache occurred in 6.3% of the patients, all of whom were having cerebral examinations.

Dosage and Administration

Mechanical or hand injection can be used to administer one or more bolus intra-arterial injections of OMNIPAQUE 140. The volume and rate of injection will depend on the type of equipment, technique used, and the vascular area to be visualized. The following volumes and rates of injection have been used with OMNIPAQUE 140.

Arteries	Volume/Injection (mL)	Rate of Injection (mL/sec)
Aorta	20-45	8-20
Carotid	5-10	3-6
Femoral	9-20	3-6
Vertebral	4-10	2-8
Renal	6-12	3-6
Other Branches of the Aorta (includes subclavian, axillary, innominate and iliac)	8-25	3-10

PERIPHERAL ANGIOGRAPHY

OMNIPAQUE 300 at a concentration of 300 mgI/mL or OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in adults for use in peripheral arteriography. OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in adults for use in peripheral venography.

Sedative medication may be employed prior to use. Anesthesia is not considered necessary.

Patient discomfort during and immediately following injection is substantially less than that following injection of various other contrast media. Moderate to severe discomfort is very unusual.

Precautions

Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all. (See PRECAUTIONS—General.)

Adverse Reactions

A transient sensation of mild warmth is usual, immediately following injection. This has not interfered with the procedure.

In phlebography the incidence of leg pain was 21%. This usually was mild and lasted a short time after injection. (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The volume required will depend on the size, flow rate, and disease state of the injected vessel and on the size and condition of the patient, as well as the imaging technique used.

OMNIPAQUE (iohexol) Injection

The dosage recommended for use in peripheral angiography is as follows:

Aortofemoral runoffs:	20 mL to 70 mL of OMNIPAQUE 350 (350 mgI/mL)
	30 mL to 90 mL of OMNIPAQUE 300 (300 mgI/mL)

Selective arteriograms:	10 mL to 30 mL of OMNIPAQUE 350 (350 mgI/mL)
(femoral/iliac)	10 mL to 60 mL of OMNIPAQUE 300 (300 mgI/mL)

Venography (per leg):	20 mL to 150 mL of OMNIPAQUE 240 (240 mgI/mL)
	40 mL to 100 mL of OMNIPAQUE 300 (300 mgI/mL)

EXCRETORY UROGRAPHY

OMNIPAQUE 300 at a concentration of 300 mgI/mL or OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated for use in adults in excretory urography to provide diagnostic contrast of the urinary tract.

OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in children for excretory urography. (See Section III for information on voiding cystourethrography.)

For pharmacokinetics of excretion in adults, see CLINICAL PHARMACOLOGY—Intravascular.

Precautions

Preparatory dehydration is not recommended in the elderly, infants, young children, diabetic or azotemic patients, or in patients with suspected myelomatosis.

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

Since there is a possibility of temporary suppression of urine formation, it is recommended that a suitable interval elapse before excretory urography is repeated, especially in patients with unilateral or bilateral reduction in renal function. (See PRECAUTIONS—General.)

Adverse Reactions

See ADVERSE REACTIONS: Intravascular—General.

Dosage and Administration

Adults: OMNIPAQUE 300 and OMNIPAQUE 350 at dosages from 200 mgI/kg body weight to 350 mgI/kg body weight have produced diagnostic opacification of the excretory system in patients with normal renal function.

Pediatrics

Excretory Urography

OMNIPAQUE 300 at doses of 0.5 mL/kg to 3.0 mL/kg of body weight has produced diagnostic opacification of the excretory tract. The usual dose for children is 1.0 mL/kg to 1.5 mL/kg. Dosage for infants and children should be administered in proportion to age and body weight. The total administered dose should not exceed 3 mL/kg.

SECTION III

CLINICAL PHARMACOLOGY—Oral/Body Cavity Use

For most body cavities, the injected iohexol is absorbed into the surrounding tissue and eliminated by the kidneys and bowel as previously described in SECTION II, CLINICAL PHARMACOLOGY—Intravascular. Examinations of the uterus (hysterosalpingography) and bladder (voiding cystourethrography) involve the almost immediate drainage of contrast medium from the cavity upon conclusion of the radiographic procedure.

Orally administered iohexol is very poorly absorbed from the normal gastrointestinal tract. Only 0.1 to 0.5 percent of the oral dose was excreted by the kidneys. This amount may increase in the presence of bowel perforation or bowel obstruction. Iohexol is well tolerated and readily absorbed if leakage into the peritoneal cavity occurs.

Visualization of the joint spaces, uterus, fallopian tubes, peritoneal herniations, pancreatic and bile ducts, and bladder can be accomplished by direct injection of contrast medium into the region to be studied. The use of appropriate iodine concentrations assures diagnostic density.

Orally administered OMNIPAQUE produces good visualization of the gastrointestinal tract. OMNIPAQUE is particularly useful when barium sulfate is contraindicated as in patients with suspected bowel perforation or those where aspiration of contrast medium is a possibility.

INDICATIONS AND USAGE, GENERAL—Oral/Body Cavity Use

OMNIPAQUE 240, OMNIPAQUE 300, and OMNIPAQUE 350 have osmolalities from approximately 1.8 to 3.0 times that of plasma (285 mOsm/kg water) and are hypertonic under conditions of use.

Adults: OMNIPAQUE 350 is indicated in adults for arthrography and oral pass-thru examination of the gastrointestinal tract.

OMNIPAQUE 300 is indicated in adults for arthrography and hysterosalpingography.

OMNIPAQUE 240 is indicated in adults for arthrography, endoscopic retrograde pancreatography and cholangiopancreatography, herniography, and hysterosalpingography.

OMNIPAQUE diluted to concentrations from 6 mgI/mL to 9 mgI/mL administered orally in conjunction with OMNIPAQUE 300 at a concentration of 300 mgI/mL administered intravenously is indicated in adults for contrast enhanced computed tomography of the abdomen.

Children: OMNIPAQUE 300 is indicated in children for examination of the gastrointestinal tract.

OMNIPAQUE 240 is indicated in children for examination of the gastrointestinal tract.

OMNIPAQUE 180 is indicated in children for examination of the gastrointestinal tract.

OMNIPAQUE diluted to concentrations from 50 mgI/mL to 100 mgI/mL is indicated in children for voiding cystourethrography.

OMNIPAQUE diluted to concentrations from 9 mgI/mL to 21 mgI/mL administered orally in conjunction with OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL administered intravenously is indicated in children for use in contrast enhanced computed tomography of the abdomen.

CONTRAINDICATIONS

OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS—General

See SECTION II, WARNINGS—General.

PRECAUTIONS—General

See SECTION II, PRECAUTIONS—General.

Orally administered hypertonic contrast media draw fluid into the intestines which, if severe enough, could result in hypovolemia. Likewise, in infants and young children, the occurrence of diarrhea may result in hypovolemia. Plasma fluid loss may be sufficient to cause a shock-like state which, if untreated, could be dangerous. This is especially pertinent to the elderly, cachectic patients of any age as well as infants and small children.

ADVERSE REACTIONS: Oral/Body Cavity Use—General

Body Cavities

In controlled clinical trials involving 285 adult patients for various body cavity examinations using OMNIPAQUE 240, 300, and 350, the following adverse reactions were reported.

Cardiovascular System

Incidence > 1%: None

Incidence ≤ 1%: Hypertension

Nervous System

Incidence > 1%: Pain (26%)

Incidence ≤ 1%: Headache, somnolence, fever, muscle weakness, burning, unwell feeling, tremors, lightheadedness, syncope

Respiratory System

None

Gastrointestinal System

Incidence > 1%: None

Incidence ≤ 1%: Flatulence, diarrhea, nausea, vomiting, abdominal pressure

Skin and Appendages

Incidence > 1%: Swelling (22%), heat (7%)

Incidence ≤ 1%: Hematoma at injection site

The most frequent reactions, pain and swelling, were almost exclusively reported after arthrography and were generally related to the procedure rather than the contrast medium. Gastrointestinal reactions were almost exclusively reported after oral pass-thru examinations. For additional information on adverse reactions that may be expected with specific procedures, see INDIVIDUAL INDICATIONS AND USAGE. For information on general adverse reactions to contrast media, see SECTION II, ADVERSE REACTIONS: Intravascular—General.

No adverse reactions associated with the use of OMNIPAQUE for VCU procedures were reported in 51 pediatric patients studied.

Oral Use

See INDIVIDUAL INDICATIONS AND USAGE: Oral Use—Adverse Reactions.

OVERDOSAGE

See also SECTION II, OVERDOSAGE.

The recommended dose of OMNIPAQUE 350 at a concentration of 350 mgI/mL for adult oral pass-thru examination of the gastrointestinal tract is 50 mL to 100 mL. In a Phase I study, 150 mL of OMNIPAQUE 350 was administered orally to 11 healthy male subjects. The incidence of diarrhea was 91% (10 of 11) and abdominal cramping was 27% (3 of 11). Despite all of these events being mild and transient the occurrences were more than double that seen at the recommended doses. It is apparent from this finding that larger volumes of hypertonic contrast media, like OMNIPAQUE, increase the osmotic load in the bowel, which may result in greater fluid shifts.

DOSAGE AND ADMINISTRATION—General

See SECTION II, DOSAGE AND ADMINISTRATION—General.

INDIVIDUAL INDICATIONS AND USAGE

Oral Use

Adults: OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in adults for use in oral pass-thru examination of the gastrointestinal tract.

OMNIPAQUE diluted to concentrations from 6 mgI/mL to 9 mgI/mL administered orally in conjunction with OMNIPAQUE 300 at a concentration of 300 mgI/mL administered intravenously is indicated in adults for use in contrast enhanced computed tomography of the abdomen. Dilute oral plus intravenous OMNIPAQUE may be useful when unenhanced imaging does not provide sufficient delineation between normal loops of the bowel and adjacent organs or areas of suspected pathology.

Children: OMNIPAQUE 300 at a concentration of 300 mgI/mL administered orally or rectally is indicated in children for use in examination of the gastrointestinal tract.

OMNIPAQUE 240 at a concentration of 240 mgI/mL administered orally or rectally is indicated in children for use in examination of the gastrointestinal tract.

OMNIPAQUE 180 at a concentration of 180 mgI/mL administered orally or rectally is indicated in children for use in examination of the gastrointestinal tract.

OMNIPAQUE diluted to concentrations from 9 mgI/mL to 21 mgI/mL administered orally in conjunction with OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL administered intravenously is indicated in children for use in contrast enhanced computed tomography of the abdomen.

Precautions

See PRECAUTIONS—General.

Adverse Reactions

Oral administration of OMNIPAQUE is most often associated with mild, transient diarrhea especially when high concentrations and large volumes are administered. Nausea, vomiting, and moderate diarrhea have also been reported following orally administered OMNIPAQUE, but much less frequently. For CT examinations using dilute oral plus intravenous contrast medium, adverse events are more likely to be associated with the intravenous injection than the hypotonic oral solution. It should be noted that serious or anaphylactoid reactions that may occur with intravascular iodinated media are possible following administration by other routes.

Adults: In controlled clinical trials involving 54 adult patients for oral pass-thru examination of the gastrointestinal tract using OMNIPAQUE 350, the following adverse reactions were reported: diarrhea (42%), nausea (15%), vomiting (11%), abdominal pain (7%), flatulence (2%), and headache (2%).

In controlled clinical studies involving 44 adult patients for dilute oral plus intravenous CT examination of the gastrointestinal tract using OMNIPAQUE 300, adverse reactions were limited to a single report of vomiting (2%).

Children: In controlled clinical studies involving 58 pediatric patients for examination of the gastrointestinal tract at concentrations of 180 and 300 mgI/mL, the following adverse reactions were reported: diarrhea (36%), vomiting (9%), nausea (5%), fever (5%), hypotension (2%), abdominal pain (2%), and urticaria (2%). In clinical studies an increased frequency and severity of diarrhea was noted with an increase in the administered concentration and dose of the radiocontrast agent.

In controlled clinical studies involving 69 pediatric patients for dilute oral plus intravenous CT examination of the gastrointestinal tract using OMNIPAQUE 240 and OMNIPAQUE 300, adverse reactions were limited to a single report of vomiting (1.4%).

Dosage and Administration

Adults: The recommended dosage of undiluted OMNIPAQUE 350 at a concentration of 350 mgI/mL for oral pass-thru examination of the gastrointestinal tract in adults is 50 mL to 100 mL depending on the nature of the examination and the size of the patient.

The recommended oral dosage of OMNIPAQUE diluted to concentrations of 6 mgI/mL to 9 mgI/mL for contrast enhanced computed tomography of the abdomen in adults is 500 mL to 1000 mL. Smaller administered volumes are needed as the concentration of the final solution is increased (see Table below). In conjunction with dilute oral administration, the recommended dosage of OMNIPAQUE 300 administered intravenously is 100 mL to 150 mL. The oral dose is administered about 20 to 40 minutes prior to the intravenous dose and image acquisition.

Children: The dosage of undiluted OMNIPAQUE 300 at a concentration of 300 mgI/mL, OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 180 at a concentration of 180 mgI/mL for oral pass-thru examination of the gastrointestinal tract in children is dependent on the nature of the examination and the size of the patient. Based on clinical experience, it is recommended that OMNIPAQUE 180 be used in children less than 3 months of age. OMNIPAQUE 180, OMNIPAQUE 240 or OMNIPAQUE 300 may be used in children 3 months of age and older. The following dosage guidelines are recommended:

Age	Volume of OMNIPAQUE
Less than 3 months	5 – 30 mL
Three months to 3 years	Up to 60 mL
Four years to 10 years	Up to 80 mL
Greater than 10 years	Up to 100 mL

When given rectally, larger volumes may be used.

OMNIPAQUE (iohexol) Injection

The recommended oral dosage of OMNIPAQUE diluted to concentrations of 9 mgI/mL to 21 mgI/mL for contrast enhanced computed tomography of the abdomen in children is 180 mL to 750 mL. Smaller administered volumes are needed as the concentration of the final solution is increased (see Table below). The total oral dose in grams of iodine should generally not exceed 5 gI for children under 3 years of age and 10 gI for children from 3 to 18 years of age. The oral dosage may be given all at once or over a period of 30 to 45 minutes if there is difficulty in consuming the required volume.

In conjunction with dilute oral administration the recommended dosage of OMNIPAQUE 240 and OMNIPAQUE 300 is 2.0 mL/kg when administered intravenously with a range of 1.0 mL/kg to 2.0 mL/kg. Dosage for infants and children should be administered in proportion to age and body weight. The total intravenously administered dose should not exceed 3 mL/kg. The oral dose is administered about 30 to 60 minutes prior to the intravenous dose and image acquisition.

OMNIPAQUE may be diluted with water or beverage as follows:

To Achieve	Add		To
One Liter of Contrast Medium at A Final Concentration (mgI/mL) of	Stock Concentration of OMNIPAQUE (mgI/mL)	Volume (mL)	Water, Carbonated Beverage, Milk, or Juice (mL)
6	240	25	975
	300	20	980
	350	17	983
9	240	38	962
	300	30	970
	350	26	974
12	240	50	950
	300	40	960
	350	35	965
15	240	63	937
	300	50	950
	350	43	957
18	240	75	925
	300	60	940
	350	52	948
21	240	88	912
	300	70	930
	350	60	940

Dilutions of OMNIPAQUE should be prepared just prior to use and any unused portion discarded after the procedure.

VOIDING CYSTOURETHROGRAPHY (VCU)

OMNIPAQUE diluted to concentrations from 50 mgI/mL to 100 mgI/mL is indicated in children for voiding cystourethrography. VCUs are often performed in conjunction with excretory urography.

Precautions

See PRECAUTIONS—General.

Since the VCU procedure requires instrumentation, special precautions should be observed in those patients known to have an acute urinary tract infection. Filling of the bladder should be done at a steady rate, exercising caution to avoid excessive pressure. Sterile procedures are essential.

Adverse Reactions

See ADVERSE REACTIONS—General.

Dosage and Administration

OMNIPAQUE may be diluted, utilizing aseptic technique, with Sterile Water for Injection to a concentration of 50 mgI/mL to 100 mgI/mL for voiding cystourethrography. The concentration may vary depending upon the patient's size and age and also with the technique and equipment used. Sufficient volume of contrast medium should be administered to adequately fill the bladder. The usual volume ranges from 50 mL to 300 mL of OMNIPAQUE at a concentration of 100 mgI/mL and 50 mL to 600 mL of OMNIPAQUE at a concentration of 50 mgI/mL.

OMNIPAQUE may be diluted with Sterile Water for Injection as indicated in the table below:

OMNIPAQUE (iohexol) Injection

To Achieve	Add To		
A Final Concentration	Each 100 mL of OMNIPAQUE Sterile Water for Injection, USP (mL)		
(mgI/mL)	OMNIPAQUE 240	OMNIPAQUE 300	OMNIPAQUE 350
100	140	200	250
90	167	233	289
80	200	275	338
70	243	330	400
60	300	400	483
50	380	500	600

Dilutions of OMNIPAQUE should be prepared just prior to use and any unused portion discarded after the procedure.

ARTHROGRAPHY

OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL or OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in radiography of the knee joint in adults, and OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in radiography of the shoulder joint in adults, and OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in radiography of the temporomandibular joint in adults. Arthrography may be helpful in the diagnosis of posttraumatic or degenerative joint diseases, synovial rupture, the visualization of communicating bursae or cysts, and in meniscography.

Precautions

See PRECAUTIONS—General.

Strict aseptic technique is required to prevent infection. Fluoroscopic control should be used to ensure proper needle placement, prevent extracapsular injection, and prevent dilution of contrast medium. Undue pressure should not be exerted during injection.

Adverse Reactions

Injection of OMNIPAQUE into the joint is associated with transient discomfort, ie, pain, swelling. However, delayed, severe or persistent discomfort may occur occasionally. Severe pain may often result from undue use of pressure or the injection of large volumes. Joint swelling after injection is less with OMNIPAQUE than with high osmolar ionic contrast medium. These types of reactions are generally procedurally dependent and of greater frequency when double-contrast technique is employed.

Nervous system: Swelling sensation (42%), pain (29%), heat sensation (13%), and muscle weakness (0.7%).

Skin and appendages: Hematoma at injection site (0.7%).

Dosage and Administration

Arthrography is usually performed under local anesthesia. The amount of OMNIPAQUE injected is dependent on the size of the joint to be examined and the technique employed. Lower volumes of contrast medium are usually injected for knee and shoulder arthrography when double-contrast examinations using 15 mL to 100 mL of air are performed.

The following concentrations and volumes are recommended for normal adult knee, shoulder, and temporomandibular joints but should serve as guidelines since joints may require more or less contrast medium for optimal visualization.

KNEE		} Lower volumes recommended for double-contrast examinations; higher volumes recommended for single-contrast examinations.
OMNIPAQUE 240	5 mL to 15 mL	
OMNIPAQUE 300	5 mL to 15 mL	
OMNIPAQUE 350	5 mL to 10 mL	
SHOULDER		} Lower volumes recommended for single-contrast examinations.
OMNIPAQUE 300	10 mL	
OMNIPAQUE 240	3 mL	
TEMPOROMANDIBULAR		
OMNIPAQUE 300	0.5 mL to 1.0 mL	

Passive or active manipulation is used to disperse the medium throughout the joint space.

ENDOSCOPIC RETROGRADE PANCREATOGRAPHY

(ERP)/ENDOSCOPIC RETROGRADE

CHOLANGIOPANCREATOGRAPHY (ERCP)

OMNIPAQUE 240 at a concentration of 240 mgI/mL is indicated in adults for use in ERP/ERCP.

Precautions

See PRECAUTIONS—General.

Adverse Reactions

Injection of OMNIPAQUE in ERP/ERCP is associated with transient pain. However, delayed, severe or persistent pain may occur and can persist for 24 hours. The cause of the pain may be due as much to

the procedure itself as to the contrast medium injected, therefore, attention should be paid to the injection pressure and total volume injected to minimize disruptive distention of the ducts examined.

Cardiovascular system: Hypertension (1%).

Nervous system: Pain (17%), somnolence (1%), and burning (1%).

Gastrointestinal system: Vomiting, diarrhea, and pressure, each with an individual incidence of 1%.

Dosage and Administration

The recommended dose of OMNIPAQUE 240 at a concentration of 240 mgI/mL is 10 mL to 50 mL but may vary depending on individual anatomy and/or disease state.

HYSTEROSALPINGOGRAPHY

OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in radiography of the internal group of adult female reproductive organs: ovaries, fallopian tubes, uterus, and vagina. Hysterosalpingography is utilized as a diagnostic and therapeutic modality in the treatment of infertility and other abnormal gynecological conditions.

Contraindications

The procedure should not be performed during the menstrual period or when menstrual flow is imminent, nor should it be performed when infection is present in any portion of the genital tract, including the external genitalia. The procedure is also contraindicated for pregnant women or for those in whom pregnancy is suspected. Its use is not advised for 6 months after termination of pregnancy or 30 days after conization or curettage.

Precautions

In patients with carcinoma or in those in whom the condition is suspected, caution should be exercised to avoid possible spreading of the lesion by the procedure.

Adverse Reactions

Injection of OMNIPAQUE in hysterosalpingography is associated with immediate but transient pain. The cause of the pain may be due as much to the procedure itself as to the contrast medium injected, therefore attention should be paid to the injection pressure and volume instilled to avoid disruptive distention of the uterus and fallopian tubes. Fluoroscopic monitoring is recommended.

Nervous system: Pain (49%), somnolence and fever each with an individual incidence of 3%.

Gastrointestinal system: Nausea (3%).

Dosage and Administration

The recommended dosage of OMNIPAQUE 240 is 15 mL to 20 mL and of OMNIPAQUE 300 is 15 mL to 20 mL but will vary depending on individual anatomy and/or disease state.

HERNIOGRAPHY

OMNIPAQUE 240 at a concentration of 240 mgI/mL is indicated in adults for use in herniography.

Precautions

See PRECAUTIONS—General.

Adverse Reactions

Nervous system: Pain (7%), headache (3%), and unwell feeling (3%).

Gastrointestinal system: Diarrhea (3%) and flatulence (10%).

Dosage and Administration

The recommended dosage of OMNIPAQUE 240 is 50 mL but may vary depending on individual anatomy and/or disease state.

HOW SUPPLIED

OMNIPAQUE 140

50 mL glass vial, 140 mgI/mL, boxes of 10 (NDC 0407-1401-50)

50 mL glass bottle, 140 mgI/mL, boxes of 10 (NDC 0407-1401-51)

50 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1401-52)

OMNIPAQUE 240

10 mL glass vial, 240 mgI/mL, boxes of 10 (NDC 0407-1412-10)

20 mL glass vial, 240 mgI/mL, boxes of 10 (NDC 0407-1412-20)

50 mL glass vial, 240 mgI/mL, boxes of 10 (NDC 0407-1412-50)

50 mL glass bottle, 240 mgI/mL, boxes of 10 (NDC 0407-1412-51)

50 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-30)

75 mL fill in 100 mL in +PLUSPAK™ (polymer bottle) boxes of 10 (NDC 0407-1412-32)

100 mL glass bottle, 240 mgI/mL, boxes of 10 (NDC 0407-1412-60)

100 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-33)

150 mL glass bottle, 240 mgI/mL, boxes of 10 (NDC 0407-1412-49)

150 mL fill in 200 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-34)

200 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-35)

125 mL in REDIFLO™ (prefilled cartridge), boxes of 10 (NDC 0407-1412-91) FLS-1

150 mL in REDIFLO™ (prefilled cartridge), boxes of 10 (NDC 0407-1412-90) FLS-1

OMNIPAQUE 300

10 mL glass vial, 300 mgI/mL, boxes of 10 (NDC 0407-1413-10)
30 mL glass vial, 300 mgI/mL, boxes of 10 (NDC 0407-1413-30)
50 mL glass vial, 300 mgI/mL, boxes of 10 (NDC 0407-1413-50)
50 mL glass bottle, 300 mgI/mL, boxes of 10 (NDC 0407-1413-51)
50 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-61)
75 mL fill in 100 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-62)
100 mL glass bottle, 300 mgI/mL, boxes of 10 (NDC 0407-1413-60)
100 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-63)
125 mL fill in 150 mL glass bottle, 300 mgI/mL, boxes of 10 (NDC 0407-1413-53)
150 mL glass bottle, 300 mgI/mL, boxes of 10 (NDC 0407-1413-90)
150 mL fill in 200 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-65)
200 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-66)
50 mL prefilled syringe, 300 mgI/mL, boxes of 10 (NDC 0407-1413-25)
100 mL in REDIFLO™ (prefilled cartridge), boxes of 10 (NDC 0407-1413-74) FLS-2
125 mL in REDIFLO™ (prefilled cartridge), boxes of 10 (NDC 0407-1413-71) FLS-1
125 mL in REDIFLO™ (prefilled cartridge), boxes of 10 (NDC 0407-1413-75) FLS-2
150 mL in REDIFLO™ (prefilled cartridge), boxes of 10 (NDC 0407-1413-72) FLS-1
150 mL in REDIFLO™ (prefilled cartridge), boxes of 10 (NDC 0407-1413-76) FLS-2

OMNIPAQUE 350

50 mL glass vial, 350 mgI/mL, boxes of 10 (NDC 0407-1414-50)
50 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-51)
50 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-89)
75 mL fill in 100 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-90)
100 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-60)
100 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-91)
125 mL fill in 150 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-76)
150 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-03)
150 mL fill in 200 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-93)
200 mL fill in 250 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-04)
200 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-94)
250 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-80)
50 mL prefilled syringe, 350 mgI/mL, boxes of 10 (NDC 0407-1414-26)
100 mL in REDIFLO™ (prefilled cartridge), boxes of 10 (NDC 0407-1414-31) FLS-1
100 mL in REDIFLO™ (prefilled cartridge), boxes of 10 (NDC 0407-1414-36) FLS-2
125 mL in REDIFLO™ (prefilled cartridge), boxes of 10 (NDC 0407-1414-37) FLS-2

REDIFLO™ (prefilled cartridges) FLS-1 are supplied with connector tubing.

REDIFLO™ (prefilled cartridges) FLS-1 are covered under one or more of the following U.S. Patents Numbers: 5,383,858, 5,997,502, 6,322,535, and 6,402,718.

REDIFLO™ (prefilled cartridges) FLS-2 are covered under U.S. Patents Number 6,652,489.

FEDERAL GOVERNMENT CODES

OMNIPAQUE 240

50 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-29)
100 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-26)
150 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-27)
200 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-28)

OMNIPAQUE 300

50 mL glass bottle, 300 mgI/mL, boxes of 10 (NDC 0407-1413-95)
50 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-98)
75 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-99)
100 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-91)
150 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-92)
200 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-93)

OMNIPAQUE 350

50 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-52)
100 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-53)
50 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-21)
75 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-20)
100 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-22)
150 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-23)
200 mL in +PLUSPAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-24)

OMNIPAQUE (iohexol) Injection

Protect vials and glass or polymer bottles of OMNIPAQUE from strong daylight and direct exposure to sunlight. Do not freeze. OMNIPAQUE should be stored at controlled room temperature, 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

OMNIPAQUE Injection in all presentations may be stored in a contrast media warmer for up to one month at 37°C (98.6°F).

**SPECIAL HANDLING AND STORAGE FOR POLYMER BOTTLES ONLY:
DO NOT USE IF TAMPER-EVIDENT RING IS BROKEN OR MISSING.**

GE Healthcare



Distributed by GE Healthcare Inc.
Princeton, NJ 08540 U.S.A.

Manufactured by GE Healthcare Ireland
Cork, Ireland

OMNIPAQUE is a trademark of GE Healthcare.
GE and the GE Monogram are trademarks of General Electric Company.

Revised May 2008

1163498 USA

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 12: COLLECTION OF NAIL CLIPPINGS AND HAIR SAMPLES

12.1 BACKGROUND

Acute exposure to high levels of some heavy metals is known to be nephrotoxic. However, the effects of chronic exposure to lower levels of such metals on renal function are unclear. Several biomarkers are potentially available for measuring heavy metal exposure in serum, urine, nails and hair. The handling of nail clippings and hair samples is easier and may be less subject to contamination than serum or urine. Heavy metal levels found within nails and hair have been validated and used for several trace elements, such as selenium, arsenic, mercury, iron, copper and zinc.

12.2 DATA COLLECTION

Data collection of nail clippings and hair samples will occur at 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 (i.e., at visit 2). In addition, toe nail clippings will be collected at Visit 4. 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 (i.e., visit 4).

12.3 ELIGIBILITY CRITERIA

12.3.1 Nail Treatments

- ***Required Number of Nail Clippings***
Whenever possible, clip no more than 10 nails or as many nails as possible. FINGERNAILS AND TOENAILS SHOULD NOT BE COLLECTED IN THE SAME CRYOVIAL; the Study Coordinator must choose one or the other. If the participant has a few long nails, he/she may clip a large amount of one nail (i.e., clip one nail several times), rather than a small amount of each nail.
- ***Nail Polish***
We prefer if the participants do not wear nail polish to the study visit; however painted nail clippings will be accepted. Other nail treatments such as nail glue and nail strengtheners are acceptable.
- ***Acrylic Nails***
Acrylic nails are not acceptable. The participant should be asked to provide toenail clippings instead.
- ***Nail Fungus or Discoloration***
The participant may still participate as long as the procedure does not cause pain or discomfort.

12.3.2 Hair Treatments

- ***Permed, Dyed, Colored or Chemically Altered Hair***

Hair analysis is only valid for natural, untreated and undamaged hair. We strongly recommend that the participants use Johnson and Johnson No More Tears® shampoo for at least two weeks before their study visit. This may help to remove extraneous elements that may be placed in the hair by other shampoos.

- ***Homogenized Hair Samples***

The participant's hair must be cut from the same area of the head to ensure the validity of the analysis. Cuts taken from different areas of the head may reflect different time periods of exposure.

12.4 OVERVIEW OF DATA COLLECTION PROCEDURES

12.4.1 Study Materials for the Collection of Nail Clippings and Hair Samples

Each clinical site will be provided with the following materials:

- ***Instructions for the Study Coordinator***

These instructions will guide the Study Coordinator through the data collection process. Please see Figure 1 for nail clipping instructions and Figure 2 for hair collection instructions.

- ***Specimen Collection Form (L02, L21 and L41)***

This form contains questions regarding the type of nail clippings provided (fingernail or toenail) and the number of nails clipped from each finger or toe. In addition, this form contains questions regarding the number of hairs extracted and the location where the hair was cut (e.g., **occipital** region).

- ***Starter Package Materials Sent by the CCCs***

- ***Stainless Steel Nail Clippers***

The nail clippers provided in the grooming kit are 100% stainless steel to avoid contamination by other heavy metals. Use the small nail clippers (Figure 1A) for the younger children and the larger nail clippers (Figure 1B) for the older children.

Figure 1A:
Use for Younger Children



Figure 1B:
Use for Older Children



- ***Stainless Steel Scissors***
The scissors provided in the grooming kit are 100% stainless steel to avoid contamination by other heavy metals.
- ***Ambient Kit Sent by the Central BioChemistry Laboratory (CBL)***
 - ***2 Labels with KID ID # and Specimen Collection Date***
 - First label will be used to distinguish the **distal** end of the hair
 - An additional label is provided for use if needed
 - ***Standard Aluminum Foil for Hair Sample (4 X 4)***
 - ***One Small Ziplock Plastic Bag (4 X 4) to Collect Hair Samples***
Note: Colored Ziplock bags are not acceptable.
 - ***½ g Silica Gel Desiccant with Pellets (Figure 1C)***

Figure 1C:



- ***2 mL Cryovial to Collect Nail Clippings***
- ***One Small Ziplock Plastic Bag (2.5 X 3) for Cryovial***
- ***Additional Materials needed to collect hair samples and nail clippings (Not Provided by CKiD)***
 - Powder-free gloves
 - SaniZide Plus Disinfectant (provided as a replacement for Simple Green D, See Figure 1D and Section 12.11 for Material Safety Data Sheet (MSDS).) The proper disposal of Simple Green D is provided in Section 12.12.
 - Hair Clips (optional)

Figure 1D:



12.4.2 Instructions for the Collection of Nail Clippings

1. Participants should be asked to refrain from cutting their nails and wearing nail polish prior to the study visit (V1b, V2 or V4).
2. Clean the blades of the clippers with the SaniZide Plus prior to use. Study Coordinators must only use the nail clippers that are provided, because they are specifically designed to minimize contamination by other heavy metals.
3. Clip the participant's nails using the provided clippers. Use the smaller (pediatric size) clippers for younger children and the larger clippers for older children. **For V1b/V2 visits**, Study Coordinators should clip all 10 fingernails, removing approximately 1 millimeter from each nail. Do not worry if the participant has clipped his/her fingernails within the last week or so – only thin slivers (approximately 1mm) are needed.

For V4 visits, ONLY TOE NAIL CLIPPINGS SHOULD BE COLLECTED.

- To use the clipper, lift the large lever up. Underneath this will be a smaller lever; flip this over forming a closed compartment to capture the nail clippings. Then, flip the large lever back to its original position. (See Figure 2)

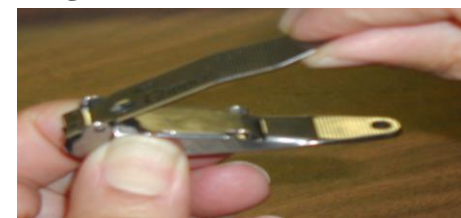
Figure 2A



Figure 2B



Figure 2C



- While clipping the nails, place the participant's hands over a flat surface and hold the nail clipper level to the surface.



- After clipping the participant's nails, reverse the small lever.
4. Carefully place the nail clippings into the 2 mL cryovial.
 5. Place cryovial into the small Ziplock bag (2.5 X 3).

At V1b/V2, the collection of fingernails is preferred. If the participant cannot provide fingernail clippings; the Study Coordinator may clip the participant's toenails instead. Again, **FINGERNAILS AND TOENAILS SHOULD NOT BE COLLECTED IN THE SAME CRYOVIAL; the Study Coordinator must choose one or the other.** However, for V4, ONLY TOE NAIL CLIPPINGS SHOULD BE COLLECTED.

12.4.3 Instructions for the Collection of Hair Samples

1. Clean the blades of the scissors with the SaniZide Plus and allow the blades to completely dry prior to use.
2. Use powder-free gloves.
3. Lift up the top layer of hair from the **occipital** region of the scalp (See Figure 2A). A hair clip can be used to keep this top layer of hair out of the way. Isolate a small thatch of hair (at least 20 fibers of hair) from *underneath* this top layer of hair from the **occipital** region. (See Figure 2B).
4. Place the label with the participant's KID ID tightly around the hair fibers located at the **distal** end (furthest away from the scalp). It is very important to place the label at the **distal** end as this will distinguish the scalp end from the **distal** end. (See Figure 2C).
5. Cut the small hair sample off the participant's head *as close to the scalp as possible* (See Figure 2D). The label must stay tightly around the thatch of hair; therefore distinguishing the **distal** end from the scalp.
6. Place the cut thatch of hair inside the aluminum foil (4 X 4) and fold the top of the aluminum foil to completely enclose the thatch of hair.
7. Place the piece of aluminum foil inside a Ziplock bag with a dessicant bag in it and seal.
8. After using the scissors, soak in SaniZide Plus.



Occipital Region of Scalp



Place the KID ID label tightly around all 20 strands.



Cut the hair sample off the participant's head *as close to the scalp as possible*

12.5 STORAGE OF NAIL CLIPPINGS

The cryovial containing the nail clippings will be stored at room temperature in a dry environment at each clinical site prior to shipment.

12.6 STORAGE OF HAIR SAMPLES

Hair samples should be kept at room temperature and in a dark place at each clinical site prior to shipment.

12.7 SPECIMEN COLLECTION FORM (L02, L21 or L41)

Each clinical site should keep a copy of this form for their records and send the original form to their designated Clinical Coordinating Center (CCC) for data entry.

12.8 SHIPMENT TRACKING FORM (ST03b)

After the completed study visit, the clinical site must complete the Shipment Tracking Form (ST03b) and include a copy of the form in the ambient kit with the nail clippings and hair sample to be sent to the NIDDK BR for storage. In addition, a copy of this form must be sent to the clinical site's designated CCC for data entry.

12.9 SHIPMENT OF NAIL CLIPPINGS AND HAIR SAMPLES

After the completed study visit, the clinical site must send the ambient kit with the ST03b form, nail clippings and hair sample to the NIDDK BR for storage. Complete the "Online Shipping Form" on the CKiD Website to notify the NIDDK BR and KIDMAC that sample(s) have been shipped to the NIDDK BR. Their contact information listed below.

12.9.1 NIDDK Biological Repository Contact Information

Sandra Ke	<i>Phone:</i> (240) 686-4703
Assistant Principal Investigator	<i>Fax:</i> (301) 515-4049
NIDDK Repository	<i>Email:</i> BIO-NIDDKRepository@thermofisher.com
Fisher BioServices	
20301 Century Blvd., Bldg. 6, Suite 400	
Germantown, MD 20874	

12.9.2 Data Coordinating Center (KIDMAC) Contact Information

Judith Jerry-Fluker	<i>Phone :</i> (410) 614-1277
KIDMAC Project Director	<i>Fax :</i> (410) 955-7587
Bloomberg School of Public Health	<i>Email :</i> jjerry@jhsph.edu
Johns Hopkins University	
615 N. Wolfe Street, E7007	
Baltimore, MD 21205	

12.10 ANALYSIS OF NAIL CLIPPINGS AND HAIR SAMPLES

Nail clippings and hair sample analyses will be performed.

12.11 MATERIAL SAFETY DATA SHEET (MSDS) FOR SANIZIDE PLUS

MATERIAL SAFETY DATA SHEET

SAFETEC OF AMERICA	May be used to comply with OSHA's Hazard Communication Standard 29 CFR 1910.1200. Standard must be consulted for specific requirements.			
	HMS HAZARD RATING			
	HEALTH	1	0 = INSIGNIFICANT	3 = HIGH
	FLAMMABILITY	0	1 = SLIGHT	4 = EXTREME
	REACTIVITY	0	2 = MODERATE	
TRANSPORTATION INFORMATION				
PROPER SHIPPING NAME		Not regulated		
HAZARD CLASS/PKG. GRP.		None/None	REF.	Not Applicable
IDENTIFICATION NUMBER		None	LABEL	None Required

SECTION 1 - PRODUCT / COMPANY IDENTIFICATION

IDENTITY (AS USED ON LABEL AND LIST)		Page 1 of 2
SaniZide Plus Germicidal Solution		
MANUFACTURER'S NAME	EMERGENCY TELEPHONE NUMBER (24 Hours)	
Safetec of America, Inc.	(800) 255-3924	
ADDRESS (NUMBER, STREET, P.O. BOX)	TELEPHONE NUMBER FOR INFORMATION	
887 Kensington Ave.	(716) 895-1822	
(CITY, STATE AND ZIP CODE)	DATE PREPARED	September 1, 2010
Buffalo, NY 14215	SUPERSEDES	January 27, 2009

SECTION 2 - HAZARDOUS INGREDIENTS / IDENTITY INFORMATION

HAZARDOUS COMPONENTS (SPECIFIC CHEMICAL IDENTITY; COMMON NAME(S))	CAS #	% (wt.) (OPTIONAL)	ACGIH TLV/TWA/STEL	
			PPM	MG/M ³
Alkyl-dimethyl-benzyl-ammonium chloride	68391-01-5	0.14	None Established	None Established
Alkyl-dimethyl-ethyl-benzyl-ammonium chloride	68956-79-6	0.14	None Established	None Established

This product is not known to contain a substance subject to Section 313 of Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA) and 40 CFR 372 at or above minimal amounts.

SECTION 3 - HEALTH HAZARD DATA

ROUTES OF ENTRY - SIGNS AND SYMPTOMS OF EXPOSURE	EMERGENCY AND FIRST AID PROCEDURES
INHALATION: Brief (minutes) inhalation will not cause adverse effects, although, constant inhalation may cause irritation to upper respiratory tract.	Remove victim to fresh air; provide oxygen if breathing is difficult; seek medical attention if required.
SKIN: Prolonged contact with skin may cause skin irritation.	Wash contaminated skin with mild soap and water; if irritation develops and persists, seek medical attention.
EYES: Brief contact to liquid or vapors may cause moderate irritation; prolonged contact may cause severe irritation associated with burning and redness.	Flush eyes with clear running water for a minimum of 2.5 minutes while holding eyelids open; if irritation persists, seek medical attention.
INGESTION: Ingestion of product may cause gastrointestinal irritation, nausea, vomiting and diarrhea.	DO NOT induce vomiting; seek immediate medical attention. Vomiting may be induced only under the supervision of a physician.

HEALTH HAZARDS (ACUTE AND CHRONIC): Acute effects are possible irritation and discomfort; no known chronic effects have been established.

CARCINOGENICITY	NTP?	No	IARC MONOGRAPHS?	No	OSHA REGULATED?	No
No additional information						

MEDICAL CONDITIONS GENERALLY AGGRAVATED BY EXPOSURE: Preexisting skin, eye, or respiratory disorders may become aggravated through prolonged exposure.

MATERIAL SAFETY DATA SHEET

IDENTITY (AS USED ON LABEL AND LIST)

SaniZide Plus Germicidal Solution

Page 2 of 2

Date: January 27, 2009

SECTION 4 - FIRE FIGHTING MEASURES

FLASH POINT (METHOD USED)

200°F (SETA)

FLAMMABLE LIMITS (% Volume in Air for Lowest Flashing Component)

LEL: Not Applicable

UEL: Not Applicable

EXTINGUISHING MEDIA

Carbon dioxide (CO₂), water, dry chemicals, synthetic foam. Type BC or ABC extinguishers.

SPECIAL FIRE FIGHTING PROCEDURES

Use self contained breathing apparatus for maximum respiratory protection. Use water spray to cool fire exposed containers and structures.

UNUSUAL FIRE AND EXPLOSIVE HAZARDS

Vapors can be heavier than air. Strong acids and bases react with aluminum to form hydrogen which is explosive if ignited.

SECTION 5 - PRECAUTIONS FOR SAFE HANDLING AND USE/LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS SPILLED OR RELEASED

Provide adequate ventilation. Spills should be collected with approved inert absorbent for disposal. Use suitable disposal containers. Material collected with absorbent may be disposed of in a permitted landfill. Report per regulatory requirements.

WASTE DISPOSAL METHODS

Dispose of in accordance with Local, State, and Federal regulations. Products classified as non-hazardous may become hazardous waste upon contact with other products. Refer to "40 CFR Protection of Environment Parts 260-299" for complete waste disposal regulations. Consult your Local, State, or Federal Environmental Protection Agency before disposing of any chemicals.

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE

Keep container(s) tightly closed when not in use. Avoid inhalation of high concentration of vapors. Store in cool, dry, well ventilated area away from possible sources of ignition sources. Keep this and other chemicals out of reach of children.

SECTION 6 - EXPOSURE CONTROLS/PERSONAL PROTECTION

RESPIRATORY PROTECTION

Ordinary, none required

VENTILATION

LOCAL EXHAUST: Recommended

MECHANICAL (GENERAL): Not required

PROTECTIVE GLOVES

Use impervious gloves to prevent prolonged contact

EYE PROTECTION

Safety glasses recommended

OTHER PROTECTIVE CLOTHING OR EQUIPMENT

Ordinary, none required

WORK/HYGIENIC PRACTICES

Practice safe work habits. Use according to label instructions.

SECTION 7 - PHYSICAL/CHEMICAL PROPERTIES

BOILING POINT

200°F

SPECIFIC GRAVITY (WATER = 1)

1.01

VAPOR PRESSURE (mm Hg)

Not determined

MELTING POINT

-1.1°C

VAPOR DENSITY (AIR = 1)

>1

pH (1% solution in water)

11-12

SOLUBILITY IN WATER

Complete

EVAPORATION RATE (n-butyl acetate = 1)

Slower than ethyl ether

APPEARANCE AND ODOR

Clear liquid

VOC, US EPA (%)

0

SECTION 8 - STABILITY AND REACTIVITY

STABILITY

UNSTABLE:

STABLE: XXX

CONDITIONS TO AVOID

Extreme temperatures

INCOMPATIBILITIES (MATERIALS TO AVOID)

Strong oxidizers; anionic materials

HAZARDOUS DECOMPOSITION OR BYPRODUCTS

Decomposition will not occur if handled/stored properly. Thermal decomposition may emit nitrous oxides, ammoniacal vapors.

HAZARDOUS POLYMERIZATION MAY OCCUR:

WILL NOT OCCUR: XXX

CONDITIONS TO AVOID

None known

The information contained herein is believed to be accurate but is not warranted to be so. Users are advised to confirm in advance of need that information is current, applicable and suited to the circumstances of use. Vendor assumes no responsibility for injury to vendee or third persons proximately caused by the material if reasonable safety procedures are not adhered to as stipulated in the data sheet. Furthermore, vendor assumes no responsibility for injury caused by abnormal use of this material even if reasonable safety procedures are followed.

12.12 PROCEDURE FOR DISPOSING SIMPLE GREEN D

1. Dilute with water and dispose by sanitary sewer.
2. Empty the container and rinse with water and offer for recycling if available in your area. Otherwise, dispose as non-hazardous waste.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY (CKiD)

SECTION 13: COGNITIVE DEVELOPMENTAL and BEHAVIORAL MEASURES

13.1 OVERVIEW

This section describes the core cognitive developmental and core behavioral procedures (cognitive-behavioral battery) that are to be performed on all children and young-adults enrolled in CKiD. The core cognitive-behavioral battery is comprised of tests measuring cognitive development/IQ, attention, executive function, behavior and health-related quality of life.

Psychologists should particularly familiarize themselves with Sections 13.2 through Sections 13.6. Information contained in Sections 13.7 and 13.8 would be useful to read.

Nephrologists and Nephrology Staff information of critical importance is located in Sections 13.6 through 13.8. Information contained in Sections 13.2 through Sections 13.5 would be useful to read.

The assessment battery will permit CKiD investigators to evaluate longitudinal changes in cognitive development, behavior functioning and Health-Related Quality of Life (HRQOL) in children and young adults with Chronic Kidney Disease (CKD).

The cognitive-behavioral battery detailed in Sections 13 was constructed to:

1. Be in accordance with the neurocognitive findings reported in the available literature on children and adolescents with CKD;
2. Be used across the wide age range proposed in this study;
3. Be administered in a straightforward fashion;
4. Be conducted in a variety of clinical settings;
5. Show minimal practice effects with the planned assessment time points.

13.2 ESTIMATED PROFESSIONAL TIME REQUIRED

Direct assessment of each child will take approximately 1.5 hours of a Psychologist's time. The amount of direct time will vary depending on the age, behavioral status, and health of the child. In addition, it is estimated that there will be another hour required for scoring, data recording, and summarization of findings for the medical chart and parent feedback report.

13.3 DESCRIPTION OF CORE COGNITIVE DEVELOPMENTAL and BEHAVIORAL MEASURES

The Core Tests for Cognitive Developmental Assessment:

- Mullen Scales of Early Learning (Mullen Scales) – 12 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
- Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV)
 - Digit Span Subtest – 6 to 16 years
- Wechsler Intelligence Scale for Children-Integrated
 - Spatial Span Subtest – 6 to 16 years

- Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) Digit Span Subtest (Forward & Reverse Components ONLY) – 17 years and older
- Wechsler Memory Scale Third Edition (WMS-III) Spatial Span Subtest - 17 years and older
- Conner’s Kiddie Continuous Performance Test (K-CPT) – 4 to 5 years
- Conner’s’ Continuous Performance Test II (CPT-II) – 6 years and older
- Delis-Kaplan Executive Function System (D-KEFS) Subtests
 - D-KEFS Tower Subtest – 6 years and older
 - D-KEFS Verbal Fluency Subtest – 6 years and older
 - D-KEFS Design Fluency Subtest – 6 years and older
 - D-KEFS Color-Word Interference Subtest – 6 years and older

The Core Tests for Behavioral Assessment:

- Behavior Assessment System for Children – 2nd Edition (BASC-2) Parent Forms 2 to 21 years
- Behavior Assessment System for Children – 2nd Edition (BASC-2) – Self-Report Form - College Version – 21 to 25 years
- Behavior Rating Inventory of Executive Function-Preschool Version–Parent Form (BRIEF-P) – 2 to 5 years
- Behavior Rating Inventory of Executive Function-Parent Form (BRIEF) – 6 to 18 years
- Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) – 18 years and older
- Pediatric Quality of Life (PedsQL)-Parent Form – 2 to 18 years
- Pediatric Quality of Life (PedsQL)-Self-Report Form – 8 to 18 years
- Pediatric Quality of Life (PedsQL)-Young Adult Form – 18 years and older

Table 13.3a: Table of responsibilities

(C)=Child completed (P)=Parent completed (YA)=Young Adult Participant completed	<u>Psychologist Administered</u>	<u>Distributed & collected by Study Coordinator & sent to CCC for scoring</u>
	√	√
CHILDREN YOUNGER THAN 6 YRS		
Mullen Scales of Early Learning (Mullen, 12-29 months) (C) or Wechsler Preschool & Primary Scale of Intelligence (WPPSI-III, 30 months-5yrs) (C)	√	
Connors’ Continuous Performance Test: Kiddie version (K-CPT, 4-5 yrs) (C)	√	
Behavior Assessment System for Children-2 (BASC2-PRS, ≥2 yrs) (P)		√
Pediatric Quality of Life Scale (PedsQL, ≥2 yrs) (P)		√
Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P, 2-5 yrs) (P)		√
CHILDREN 6 YRS OR OLDER		
Wechsler Abbreviated Scales of Intelligence Second Edition (WASI II) (C, YA)	√	
Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV, 6-16 yrs) Digit Span and Spatial Span Subtests (C)	√	
Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV, ≥ 17 yrs) Digit Span Subtest (C, YA)	√	
Wechsler Memory Scale Third Edition (WMS-III, ≥ 17 yrs) Spatial Span Subtest (C, YA)	√	
Connors’ Continuous Performance Test (CPT-II) (C)	√	
Delis-Kaplan Executive Function System (D-KEFS) Tower, Verbal Fluency, Design Fluency, Color-Word Interference Subtests (C, YA)	√	
Behavior Assessment System for Children- Parental Rating Scales (BASC2-PRS,) (P)		√
BASC-2 - Self-Report of Personality (BASC2-SRP COL,) (YA)		√
Pediatric Quality of Life Scale (PedsQL) (P,C, YA)		√
Behavior Rating Inventory of Executive Function (P, YA)		√

Table 13.3b: CKiD Cognitive/Developmental/Behavioral Tests by Participant Age & Corresponding Data Coding Sheet

PARTICIPANT AGE	TESTS	Estimated Assessment Time for Child or Young Adult	Estimated Assessment Time for Parent	Behavioral Coding Sheet	Cognitive Coding Sheet	Quality of Life PedsQL
≥ 12months and < 24months	Mullen Scales (12-29)	25 min		NA	NRCO3a	NA
≥ 24months and < 30 months	Mullen Scales (12-29) BASC-2- Parent (2-5) BRIEF-P (2-5.11) PedsQL-Parent (2-4)	25 min	15 min 25 min 5 min	NRCO4b	NRCO3a	*NRCO1a (Parent, 2-4)
≥ 30 months and < 4 years	WPPSI-III (2.6-3:11) BASC-2- Parent (2-5) BRIEF-P (2-5.11) PedsQL-Parent (2-4)	35 min	15 min 15 min 5 min	NRCO4b	NRCO3b	*NRCO1a (Parent, 2-4)
≥ 4 years and < 5 years	WPPSI-III (4.0-7.3) OR BASC-2- Parent (2-5) BRIEF-P (2-5.11) K-CPT PedsQL-Parent (2-4)	45 min 10min	15 min 15 min 5min	NRCO4b	NRCO3c	*NRCO1a (Parent, 2-4)
≥ 5 years and < 6 years	BASC-2- Parent (2-5) BRIEF-P (2-5.11) K-CPT WPPSI-III (4:0-7:3) PedsQL-Parent (5-7)	10 min 45 min	15 min 15 min 5 min	NRCO4b	NRCO3c	*NRCO1b (Parent, 5-7)
≥ 6 years and < 8 years	BASC-2- Parent (6-11) BRIEF (6-18) CPT-II D-KEFS Subtests WASI II WISC-IV Digit & Spatial Span Subtests PedsQL-Parent (5-7)	15 min 25 min 20 min 10 min	5 min 15 min 5 min	NRCO4c	NRCO3d	*NRCO1b (Parent, 5-7)
≥ 8 years and < 12 years	BASC-2-Parent (6-11) BRIEF (6-18) CPT-II D-KEFS Subtests WASI II WISC-IV Digit & Spatial Span Subtests PedsQL Parent (8-12) PedsQL Child (8-12)	15 min 25 min 20 min 10 min 5min	15 min 15 min 5 min	NRCO4d	NRCO3d	*NRCO1d (Parent, 8-12) & *NRCO1e (Child, 8-12)
≥ 12 years and < 13 years	BASC-2-Parent (12-21) BRIEF (6-18) CPT-II D-KEFS Subtests WASI II WISC-IV Digit & Spatial Span Subtests PedsQL Parent (8-12) PedsQL, Child (8-12)	15 min 25 min 20 min 10 min 5 min	15 min 15 min 5 min	NRCO4e	NRCO3d	*NRCO1d (Parent, 8-12) & *NRCO1e (Child, 8-12)
≥ 13 years and < 17 years	BASC-2-Parent (12-21) BRIEF (6-18) CPT-II D-KEFS Subtests WASI II WISC-IV Digit & Spatial Span Subtests PedsQL Parent (13-18) PedsQL Teen (13-18)	15 min 25 min 20.min 10 min 5 min	15 min 15 min 5 min	NRCO4e	NRCO3d	*NRCO1f (Parent, 13-18) & *NRCO1g (Teen, 13-18)

Table 13.3b (continued): CKiD Cognitive/Developmental/Behavioral Tests by Participant Age & Corresponding Data Coding Sheet

PARTICIPANT AGE	TESTS	Estimated Assessment Time for Child or Young Adult	Estimated Assessment Time for Parent	Behavioral Coding Sheet	Cognitive Coding Sheet	Quality of Life PedsQL
≥ 17 years and < 18 years	BASC-2-Parent (12-21) BRIEF (6-18) CPT-II D-KEFS Subtests WASI II WAIS-IV Digit Span Subtest OR WMS-III Spatial Span Subtest PedsQL Parent (13-18) PedsQL Teen (13-18)	15 min 25 min 20 min 5 min 5 min 5 min	15 min 15 min 5 min	NRC04e	NRC03e	*NRC01f (Parent, 13-18) & *NRC01g (Teen, 13-18)
≥ 18 years and < 19 years	BASC-2-Parent (12-21) BASC-2-Self report (21-25) BRIEF (6-18) OR BRIEF-A (18+) CPT-II D-KEFS Subtests WASI II WAIS-IV Digit Span Subtest OR WMS-II Spatial Span Subtest PedsQL Parent (13-18) PedsQL Young Adult (18+)	10 min 25 min 20 min 5 min 5 min 5 min	15 min 15 min 15 min 15 min	NRC04f	NRC03e	*NRC01f (Parent, 13-18) & *NRC01h (<u>Young Adult, 18+</u>)
≥ 19 years and < 21 years	BASC-2-Parent (12-21) BASC-2 Self report (21-25) BRIEF (6-18) BRIEF-A (18+) CPT-II D-KEFS Subtests WASI II WAIS-IV Digit Span Subtest OR WMS-III Spatial Span Subtest PedsQL Young Adult (18+)	15 min 15 min 15 min 10 min 25 min 20 min 5 min 5 min 5 min	15 min 15 min	NRC04f	NRC03e	*NRC01h (<u>Young Adult, 18+</u>)
≥ 21	BASC-2-Parent (12-21) BASC-2 Self-report (21-25) BRIEF-A (18+) CPT-II D-KEFS Subtests WASI II WAIS-IV Digit Span Subtest WMS-III Spatial Span Subtest PedsQL Young Adult (18+)	15 min 15 min 15 min 25 min 20 min 5 min 5 min 5 min	15 min	NRC04g	NRC03e	*NRC01h (<u>Young Adult, 18+</u>)

* Peds QL NEPHRON Data Entry Form

* Peds QL given to youth and parents by study coordinator

Diagram 13.3.a CKiD Cognitive and Development Tests by Chronological Age

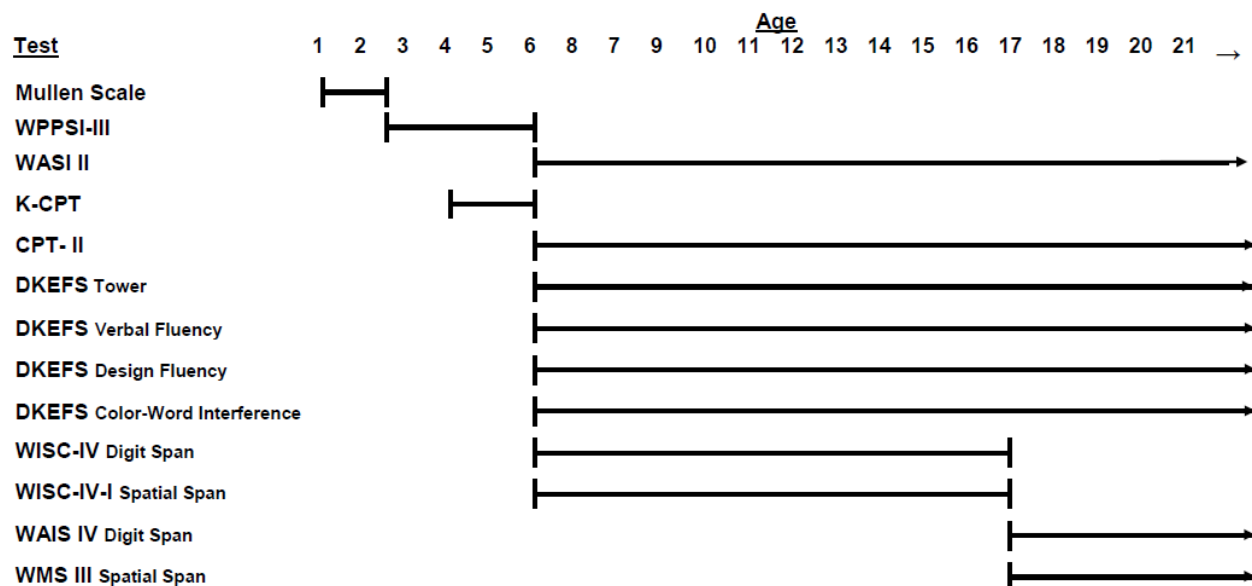
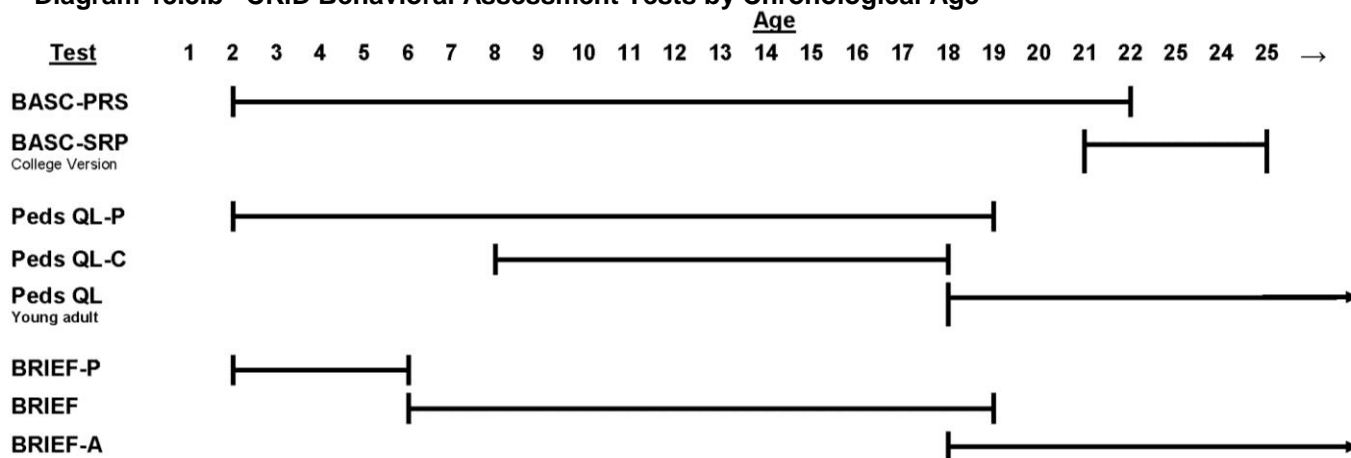


Diagram 13.3.b CKiD Behavioral Assessment Tests by Chronological Age



13.4 TASKS ADMINISTERED BY THE PSYCHOLOGIST

13.4.1 Mullen Scales of Early Learning

Children between the ages of 12 months through 29 months will be administered the Mullen Scales of Early Learning. The Mullen Scales of Early Learning is a comprehensive measure of cognitive function for children, from birth to 68 months, so we should have adequate floors and ceilings for the targeted age range. 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 development/intelligence. The Mullen is simple to administer for those with early childhood experience and has standardized instructions for each item. Test administration requires a test kit which contains all the necessary items and materials for use during the assessment.

13.4.2 Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III)

Children between the ages of 2.5 through 5 years, will be administered the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III). The WPPSI-III is a measure of general intelligence that has been thoroughly revised to address issues of developmental sensitivity. The test has two forms: WPPSI-III 2:6-3:11 and WPPSI-III 4:0-7:3. Although the test is applicable for children up to 7 years of age, the WPPSI will be administered for children younger than age 6. The WPPSI-III, for children between the ages of 2 years 6 months through 3 years 11 months, includes four core subtests: Receptive Vocabulary, Information, Block Design, and Object Assembly. The older version of the WPPSI-III, for children between the ages of 4 years through 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.

13.4.3 Wechsler Abbreviated Scale of Intelligence Second Edition (WASI II)

Children 6 years of age 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.

13.4.4 Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV) Digit Span Subtest

The WISC-IV Digit Span Subtest will be administered to all children between the ages of 6 to 16 years. 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 numbers in reverse order. Age-based standard scores will be generated for the total score, forward and reverse sequences. ***Permission has been obtained from NCS Pearson, Inc. to create a WISC-IV Digit Span form for use in CKiD.

13.4.5 Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) Digit Span Subtest

The WAIS-IV Digit Span Subtest requires individuals to repeat verbally presented numbers. Only the forward and reverse components will be administered to all children 17 years of age and older. Sequencing is NOT administered. The subtest will require approximately 5 minutes to administer. Age-based standard scores will be generated for forward and reverse sequences. Total standard scores will NOT be able to be obtained because Sequencing is NOT administered. ***Permission has been obtained from NCS Pearson, Inc. to create a WAIS-IV Digit Span form for use in CKiD.

13.4.6 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 6 years of age and older. The CPT-II is used to identify visual attention problems manifested in impaired vigilance and impulsive responding. The primary stimuli are letters that are presented to a child on a computer screen. Psychologists must print the test results from the CPT-II computerized program and send to their designated Clinical Coordinating Center along with the other study forms. The test can be administered in approximately 15 minutes and provides information about the child's attention. **The results print out should be sent to CKiD.**

13.4.7 Conner's Continuous Performance Test: Kiddie Version (K-CPT)

The Conner's Continuous Performance Test: Kiddie Version (K-CPT) will be administered to all children between the ages of 4 through 5 years. The K-CPT is a computer-conducted test of attention that parallels the Conner's Continuous Performance Test Second Edition (CPT-II) described above. The K-CPT uses picture stimuli instead of letters, requires approximately 7 minutes to complete, and provides information about the child's attention. **The results print out should be sent to CKiD.**

13.4.8 Delis-Kaplan Executive Function System Subtests (D-KEFS)

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 administered to all children ages 6 years and older: Tower, Verbal Fluency, Design Fluency and Color-Word Interference. While the normative sample for the subtests actually begins at 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 function over time.

13.4.9 Wechsler Intelligence Scale for Children Fourth Edition Integrated (WISC-IV-I) Spatial Span Subtest

The WISC-IV Spatial Span Subtest will be administered to all children between the ages of 6 and 16 years. The participant is shown a board of raised blocks. The examiner touches the blocks one at a time, in sequences of increasing length, and the participant is asked to touch the blocks in the same sequence. This subtest includes both forward and backward components. Age-based standard scores will be generated for Spatial Span Forward and Spatial Span Backward.

13.4.10 Wechsler Memory Scales Third Edition (WMS-III) Spatial Span Subtest

The WMS-III Spatial Span Subtest will be administered to all participants 17 years of age and older. The participant is shown a board of raised blocks. The examiner touches the blocks one at a time, in sequences of increasing length, and the participant is asked to touch the blocks in the same sequence. This subtest includes both forward and backward components. Age-based standard scores will be generated for Spatial Span Forward and Spatial Span Backward.

Table 13.4a: Ordering information for tests in the core battery.

Test	Publisher	Estimated Site Cost of purchasing test kit & scoring manual or computer scoring program. To ensure uniformity of data collection CKiD has obtained appropriate authorization from each publisher to distribute testing forms to all collaborating sites
Kiddie Conner’s Continuous Performance Test (K-CPT)	Pearson	KCPT disk provided by CKiD. Scored by psychologist. SEND computer printout to CKiD.
Conner’s Continuous Performance Test-II (CPT-II)	Pearson	CPT disk provided by CKiD. Scored by psychologist. SEND computer printout to CKiD.
Delis-Kaplan Executive Function Systems (D-KEFS) Subtests: Tower, Verbal Fluency, Design Fluency, Color-Word Interference	Pearson	Testing forms provided by CKiD. Scored by psychologist.
Mullen Scales of Early Learning (Mullen)	Pearson	Testing forms provided by CKiD Scored by psychologist
Wechsler Abbreviated Scales of Intelligence Second Edition (WASI II)	Pearson	Testing forms provided by CKiD. Scored by psychologist.
Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) Digit Span Subtest	Pearson	Testing forms provided by CKiD. Psychologist administers and scores DS forward and SD backward only. Permission obtained from NCS Pearson to purchase per-person administrations of the Digit Span subtest for CKiD participants. Permission granted for CKiD to photocopy WAIS-IV Digit Span subtest form for use.
Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV Integrated) Digit Span and Spatial Span Subtests	Pearson	Testing forms provided by CKiD. Permission obtained from NCS Pearson, Inc. to purchase per-person administrations of the Digit and Spatial Span subtests for CKiD participants. Permission granted for CKiD to photocopy WISC-IV Digit and WISC-IV I Spatial Span subtest forms for use.
Wechsler Preschool and Primary Scales of Intelligence-III (WPPSI-III)	Pearson	Testing forms provided by CKiD. Scored by psychologist.
Behavior Assessment System for Children (BASC-2) - Parent Rating Scales and Self-report Rating Scales	Pearson	Testing forms provided by CKiD and scored by CKiD.
Behavior Rating Inventory for Executive Functions (BRIEF)	PAR	Testing forms provided by CKiD and scored by CKiD
Behavior Rating Inventory for Executive Functions - Preschool Version (BRIEF-P)	PAR	Testing forms provided by CKiD and scored by CKiD.
Pediatric Quality of Life Scale (Peds QL) - Parent , Child and Young Adult	PedsMetrics	Testing forms provided by CKiD and scored by CKiD.

13.5 ADMINISTRATION GUIDELINES

13.5.1 General Information for Psychologist Administered Tests

Prior to testing at the study visit, the Psychologist should check with the Study Coordinator to determine if the child has any impairment that might interfere with the standard administration of the tests (i.e. Question **C9** and **C10** on the **Medical History Form or F14**). It is crucial for **all personnel** who will test the children with CKD to practice administering and scoring the entire test battery prior to testing a study participant. Familiarity with the administration procedures and the testing materials is essential for achieving reliable assessment results. Some tests require simultaneous administration and scoring; in others, additional attention must be paid to scoring details. All of the tests require specific and rigorous adherence to test-developer instructions to preserve standardization.

All of the neurocognitive tasks used in this protocol are standardized; consequently, administrative scripts are provided. All instructions should be given verbatim, and instructions may be repeated when so indicated in the test manual. The entire age-appropriate neurocognitive screening battery should be completed at each scheduled testing occasion. Sometimes a participant will wish to stop during a test or wish to leave the examination altogether. Use your professional judgment in order to obtain the most valid assessment possible. Indicate the number of testing sessions on the cognitive coding data sheet.

Described below are the reliability codes that will be used to communicate the evaluator's professional judgment about the child's performance. Use the Reliability Coding Worksheet provided by CKiD and then transfer Reliability Codes to the data coding sheet.

Testing should be performed in a quiet room in which environmental distractions have been eliminated or minimized. Every effort should be made to build rapport with the child during the evaluation in order to attain maximal performance. Interruptions during the testing session should be minimized by disconnecting telephones and placing a sign on the door of the examination room indicating that testing is in progress. Appropriate sized table and chairs are required. Because several of the tests are timed, a stopwatch is also necessary. Short "breaks" may be taken to ensure participant cooperation and maximum performance.

Children with poor kidney function tend to fatigue easily. Testing should not be done on a day that the child has undergone non-routine invasive medical procedures, non-invasive medical procedures that the child perceives as disturbing or medical tests involving sedation. The Study Coordinator should be able to facilitate scheduling any procedures that could negatively influence the child's performance on the neurocognitive assessment on an alternate day. While testing would not generally be contraindicated on a day that a child received a venipuncture (as most CKD children become relatively sensitized to routine blood draws), we recommend that testing is not be done on the day that the Iohexol GFR studies are performed.

13.5.2 English Language Issues

If a CKiD participant (between the ages of 8 and older) has learning disabilities or visual problems that prevent independent completion of the self-report surveys, the Reading Assistance Procedure should be used with the child to complete the PedsQL.

In the event that the child speaks Spanish, the CCC will provide Spanish versions of the behavior rating scales if available.

Reading Assistance Administration Procedure - The reading assistant (not the parent) should have a copy of the behavioral survey and be seated in a manner that he or she can observe the respondents ability to track items that are being read out loud. The test administrator should read the directions and review the sample questions to assess the respondent's ability to comprehend the response options. The reading assistant should indicate the item number, read the question verbatim, and then ask the respondent to circle the answer of their choice. Care should be taken that the provided reading assistance does not impinge on the respondent's sense of confidentiality.

13.5.3 Qualifications of Examiner for Psychologist Administered Tests (cognitive and attention)

For the CKiD Study, we insist that all participants receive their cognitive assessment from a licensed Psychologist or from a trained examiner (i.e., technicians) or graduate student who is being closely supervised by a Licensed Psychologist. Adhering to this recommendation will facilitate quality control/quality assurance of the data obtained for the neurocognitive protocol procedures for each participant.

13.5.4 Administration Order for the Psychologist Administered Tests

Given the potential for order effects in the core battery because of fatigue issues associated with chronic kidney disease, and to counterbalance each of the blocks within and across participants, we have organized the tests into two separate blocks. In this way, we can control for any order effects in the battery and provide the examiner with flexibility in the administration of the tests within an assessment block in order to address the needs of difficult-to-evaluate participants. The CCCs are responsible for notifying the clinical site Psychologist of the order in which the blocks of tests are to be administered.

For the youngest of our participants (i.e., ages 12 months through 47 months), blocking is not an issue in that they will be receiving only the Mullen or the WPPSI-III.

For children 4 through 5 years of age, the WPPSI-III and K-CPT will be counterbalanced across study participants and time points. This can be seen in Table 13.5.4a.

For children between the ages of 6 through 16 years, the tests are divided into two blocks (See Table 13.5.4b). Block A will include two subtests of the WASI-II, the WISC-IV Digit Span Subtest and the WISC-IV I Spatial Span Subtest and Block B will include the CPT-II and four D-KEFS Subtests.

For children 17 years of age and older, the tests are divided into two blocks (See Table 13.5.4c). Block A will include two WASI II subtests, the WAIS-IV Digit Span Subtest (Forward and Backward) and the Wechsler Memory Scale Spatial Span Subtest. Block B will include the CPT-II and the four D-KEFS Subtests.

Table 13.5.4d provides the structure for counterbalancing the test block administrations across participants and assessment time points. The blocking order will be determined by the CCC. If you have any questions about the block, contact your CCC Project Director.

Table 13.5.4a Cognitive test instruments by blocks for children ages 4 to 5.

Block A
WPPSI-III
Block B
K-CPT

Table 13.5.4b Cognitive test instruments by blocks for children ages 6 to 16.

Block A
WASI II (Vocabulary & Matrix Reasoning Subtests) WISC-IV Digit Span Subtest WISC-IV-Integrated Spatial Span Subtest
Block B
CPT-II D-KEFS Tower Subtest D-KEFS Design Fluency Subtest D-KEFS Verbal Fluency Subtest D-KEFS Color-Word Subtest

Table 13.5.4c Cognitive test instruments by blocks for children 17 years and older.

Block A
WASI II (Vocabulary & Matrix Reasoning Subtests) WAIS IV Digit Span Subtest (Forward & Backward) WMS III Spatial Span Subtest
Block B
CPT-II D-KEFS Tower Subtest D-KEFS Design Fluency Subtest DKEFS Verbal Fluency Subtest D-KEFS Color-Word Subtest

Table 13.5.4d Counterbalanced administration of the assessment battery blocks for all age ranges.

Case #	Baseline Neurocognitive Visit Third Neurocognitive Visit, Fifth Neurocognitive Visit	Second Neurocognitive Visit, Fourth Neurocognitive Visit Sixth Neurocognitive Visit
Case #1	Block A then Block B	Block B then Block A
Case #2	Block B then Block A	Block A then Block B
Case #3	Block A then Block B	Block B then Block A
Case #4	Block B then Block A	Block A then Block B
Case #5	Block A then Block B	Block B then Block A
Case #6	Block B then Block A	Block A then Block B
Case 7, 9, 11 & other odd numbered cases	Block A then Block B	Block B then Block A
Case 8, 10, 12 & other even numbered cases	Block B then Block A	Block A then Block B

13.5.5 Reliability Coding for Psychologist Administered Tests

We will be employing a behavioral coding mechanism that will provide examiner perception of the reliability of the test data collected. This rating will be conducted for each task that is administered and should be completed immediately after the task is completed and recorded on CKiD Reliability Worksheet. The Reliability Code will assist CKiD in determining why a particular task was not administered, and/or if a data point should be marked in the data set because of low reliability. The coding system involves a 2-point code for each task and is described below (e.g., 1.0 for a typical reliable administration).

13.5.5.1 Reliability Codes for Each Task

Below is the two-point system to permit a rating for determining the reliability of each task. The reliability code consists of 2 digits. The second digit will capture the reason why the reliability was compromised. The second score would be recorded after the decimal point (e.g., 1.0).

13.5.5.2 Reliability Code if an Entire Measure is Not Administered

If an ENTIRE measure was not administered, please use the 2 point reliability code to reflect the reason. Below is the two-point system to permit a rating that specifies the reason why the measure was not administered. The second score is recorded after the decimal point (e.g., 5.1 indicates that the participant attempted the task but was too impaired to complete, primarily related to physical reasons/limitations).

Primary Codes:

- 1 Standard procedure, Reliable Results
- 2 Irregular Procedure, Reliability Impact Minor
(e.g., child tired, but able to complete)
- 3 Irregular Procedure, Unreliable (e.g., child too active, too ill; examiner errors)
- 4 Participant Attempted – Participant too Impaired to Complete
- 5 Participant Attempted - Examiner Discontinued
- 6 Participant Attempted - Refused to Finish
- 7 Participant Refused to Begin
- 8 Not attempted - Reason Unrelated to Participant
(e.g., examiner forgot, task or measure not available)

Secondary Codes:

- .0 Use this secondary reliability code when standard procedure with adequate reliability or irregular procedure with adequate reliability occurred.
- OR**
- .0 Testing problems not directly related to the patient (e.g., trained examiner not available, improper test administration, procedure not available).
 - .1 Testing problems primarily related to physical limitations: injuries or disabilities (not cognitive in nature).
 - .2 Testing problems primarily related to cognitive deficit: impairments in cognition, and/or behaviors of the participant.

The Reliability Recording Worksheet is located in Appendix A.

13.6 QUALITY CONTROL OF THE DATA

Data for the first two available cases completed at each clinical site will be reviewed by the regional project Psychologists (Dr. Hooper or Dr. Gerson). The regional Psychologists will communicate any identified errors that necessitate changes to previously entered data to the CCC and to the DCC. Thereafter, for approximately 25% of the sample at baseline and at each of the neurocognitive follow-up visits, the regional Psychologists will review neurocognitive protocol forms to verify administration fidelity and to perform double scoring of the protocol procedures to check the accuracy of translation of raw scores into standardized scores and the transcription of the standardized scores from the procedure protocol forms onto the correct Cognitive Coding Sheet. The regional Psychologist will initially review 2 consecutive protocols from each site to determine error trends and then review a random sample of approximately 20% of the remaining protocols.

In addition to the quality control procedures completed by the regional Psychologists, the DCC will check 10% of the baseline and follow-up visit protocols to assess the reliability of transcription from the correct Cognitive Coding Sheet onto NEPHRON, the web-based data management system. The DCC will also perform quality assurance checks for the behavioral data by checking the accuracy of data entry into the computerized scoring assistants, the transcription of the standardized scores from the computerized print-out onto the correct Behavioral Coding Sheet and the transcription from the Behavioral Coding Sheet onto NEPHRON.

13.6.1 Administration and Distribution

It is expected that all sites will have or have access to the testing procedures outlined in this section. If sites do not have specific tests or procedures, then they should contact the CCC to discuss options that will be available to them with respect to this part of the protocol. All reasonable efforts should be made to administer the complete neurocognitive battery to each study participant to ensure completeness of the study data. All testing forms and single-use protocols will be provided by CKiD.

13.6.2 Procedures for Photocopying, Transmission and Storage of Forms Used in Psychologist Administered Tests

All original testing forms must be copied by the site Psychologist OR the site Study Coordinator.

After the forms are photocopied the Study Coordinator will federal express the original forms to their designated CCC for storage. These original data forms will be maintained at the CCCs for future use as needed by the CKiD study staff. Copies of the data forms will be stored according to Institutional Review Board and HIPAA standards at your clinical site and at the discretion of the Licensed Psychologist who is serving as the CKiD neurocognitive protocol site investigator in consultation with the local CKiD study coordinator and local CKiD Pediatric Nephrologist PI. Maintaining a copy of the testing forms at the site is important and among of other things, will allow the Psychologist to review prior testing to determine significant improvement or declines in functioning.

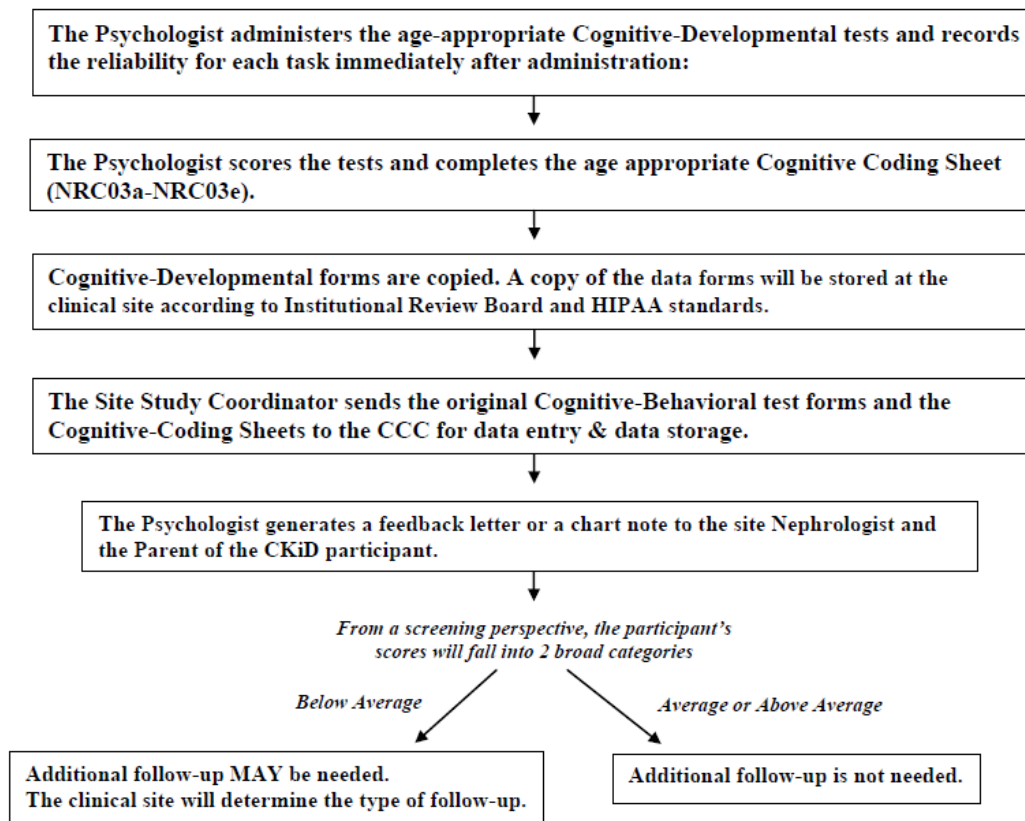
13.6.3 Scoring, Data Entry and Feedback Reports

After completing the testing session, each test should be scored by the examiner and the scores recorded onto the age appropriate Cognitive Coding Sheets (NRC03a-NRC03e). The original testing forms should not be released to parents or nephrologist without prior discussion with the site's regional psychologists. The Cognitive Coding Sheets will be provided by the CCCs. Each page of the Cognitive Coding Sheet should be reviewed and initialed by the Licensed Psychologist who has done the testing and/or who has supervised the testing to assert that the testing, data transformations and transcription of the data onto the CKiD study forms meet the standards established by the American Psychological Association regarding psychological assessment procedures. The Cognitive Coding Sheet must be sent to the clinical site's designated CCC with the ORIGINAL neurocognitive forms for data entry. A feedback letter for the participant's Nephrologist (and patient chart documentation of the testing results) and a parent feedback

letter should be generated. It is recommended that the feedback reports are completed within 4 weeks of completing the testing. Nephrologists and parents should be reminded that results by themselves should not be used to make clinical or educational decisions. A more comprehensive evaluation with a Neuropsychologist is needed to make educational decisions or decisions about mental health needs. However, in keeping with the clinical practice standards of Psychologists the parent feedback will report performance categories (Below Average, Average, Above Average) but not actual test scores. With parental permission the test scores and additional details of the testing results contained in the feedback report can be released to professionals involved with this child.

Figure 13.6.3a

COGNITIVE-DEVELOPMENTAL DATA ENTRY AND FEEDBACK



13.7 SURVEYS DISTRIBUTED AND COLLECTED BY NEPHROLOGY STAFF

13.7.1 General Information for Distribution of Behavior Rating Scales

At the Clinical Site:

It is suggested that the behavior rating scales be distributed at the beginning of the study visit by someone from the nephrology team (e.g., the Study Coordinator) and collected from the participant and/or parent prior to the end of the study visit. Some of the rating scales have age-based forms and it will be crucial to ensure that the parent and child are completing the appropriate form for the current age of the child at the TIME OF ASSESSMENT. Some of the assessments are double sided so please make sure that all items have been completed prior to the end of the study visit. Also, the nephrology team member responsible for collecting the behavior rating scales should check for all targeted “alert items” on the BASC-2 PRS using the Behavioral Alert Items Form provided by CKiD. **If any of the “critical items” are endorsed, the Study Coordinator must notify the participant’s Principal Investigator and/or Nephrologist and FAX the Behavioral Alert form (see Appendix B for a copy of the Behavioral Alert Form) to the CCC Project Director. The clinical site will determine the appropriate follow-up and communicate**

the follow-up plan to the CCC. The CCC will communicate the alert to the Regional Psychologists for their input. The CKiD study coordinator may choose to contact the CKiD Psychologist who tested the youth for advice regarding how to proceed.

At the CCC:

The CCC will data enter the behavioral forms into the appropriate scoring assistant programs. **The CCCs should give priority attention to the behavioral forms from CKiD participants who have been identified by their site as having endorsed any of the Behavioral Alert items.** The participant's Nephrologist will not receive feedback about the behavioral questionnaires unless scoring suggests a clinically significant elevation on the BASC-2 Behavior Symptom Index Scale or the Depression Subscale. In the event that the BASC-2 Behavior Symptom Index T score is ≥ 70 or the Depression Subscale T-score of ≥ 70 , a prompt will appear in NEPHRON stating that the value is out of range. The CCC data entry personnel will override the data entered value and enter the study participant's actual score. The CCC data entry personnel will also provide the CCC Project Director with the agreed upon pages of the generated summary report from the scoring assistant, which reflects a clinically significant problem that was identified during data entry. The CCC is then responsible for notifying the clinical site's CKiD Study Coordinator or PI and providing the generated summary report within a reasonable time period.

13.7.2 Behavior Assessment System for Children-2 Parent Rating Scale and Self-Report of Personality, College Version (BASC-2 PRS & BASC-2 SRP COL)

This Likert-style questionnaire uses parent and young adult participant responses to questions on a variety of topics related to social-behavioral functioning. Age-based T-Scores can be obtained for four general areas: Internalizing, Externalizing, Adaptability, and Behavior Symptoms. Scores are also obtained for twelve subtest areas: Hyperactivity, Aggression, Conduct Problems, Anxiety, Depression, Somatization, Atypicality, Withdrawal, Attention Problems, Adaptability, Social Skills, Leadership, Activities of Daily Living and Functional Communication. If a parent cannot read, then items can be read to the parent using the Reading Assistance Procedure.

13.7.3 Review of BASC-2 Parent Rating Scales and Self-Report of Personality, College Version for Endorsement of Alert Items

The BASC-2 Scales contain questions that are considered to be “**alert items**” by the CKiD project staff. The BASC-2 questionnaires need to be reviewed by the nephrology staff person responsible for collecting these inventories immediately after they have been completed by the parent and/or child **AND before the CKiD participant/parent leave.** The Behavioral Alert Items Form will allow for quick identification of the items of interest.

If any of the critical items are endorsed, the Study Coordinator will notify the participant's Principal Investigator and/or Nephrologist and FAX the Behavioral Alert form to the clinical site's designated CCC for documentation. The clinical site will determine the method of follow-up. The CKiD study coordinator may choose to contact the CKiD Psychologist who tested the youth for advice regarding how to proceed. **The CCC will communicate the alert to the Regional Psychologists for their input.**

13.7.4 Pediatric Quality of Life Scale (PedsQL)-Parent

The Pediatric Quality of Life Scale (PedsQL) will be administered to the parents of all participants between the ages of 2 through 16 years. The PedsQL is a generic health status instrument that assesses five domains of health (Physical Functioning, Emotional Functioning, Psychosocial Functioning, Social Functioning and School Functioning). Three summary scales (Physical Health, Psychosocial, and Total Summary) are generated during scoring. The inventory should take approximately 5 minutes to complete.

13.7.5 Pediatric Quality of Life Scale (PedsQL)-Child

The Pediatric Quality of Life Scale (PedsQL) will be administered to children between the ages of 8 and 17. The PedsQL is a generic health status instrument that assesses five domains of health (Physical Functioning, Emotional Functioning, Psychosocial Functioning, Social Functioning and School Functioning). Three summary scales (Physical Health, Psychosocial, and Total Summary) are generated during scoring. The inventory should take approximately 5 minutes to complete.

13.7.6 Pediatric Quality of Life Scale (PedsQL)-Young Adult

The Pediatric Quality of Life Scale (PedsQL) will be administered to participants 18 year old and older. The PedsQL is a generic health status instrument that assesses five domains of health (Physical Functioning, Emotional Functioning, Psychosocial Functioning, Social Functioning and School Functioning). Three summary scales (Physical Health, Psychosocial, and Total Summary) are generated during scoring. The inventory should take approximately 5 minutes to complete.

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

The BRIEF-P is a 63-item questionnaire for parents of preschool children between the ages of 2 through 6 that allow for the assessment of 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 response. Excellent reliability and validity has been demonstrated. It should take approximately 15 minutes to complete.

13.7.8 Behavior Rating Inventory for Executive Functions (BRIEF)

The BRIEF is an 86-item questionnaire for parents of school-age children between the ages of 6 through 18 that allow for the assessment of executive function behaviors (i.e. the ability 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, Monitoring) and three summary scales (Behavioral regulation, Metacognition and Global Executive Composite). The BRIEF incorporates two validity scales (measuring excessive negativity and inconsistency of responses) and has been shown to have excellent reliability and validity. It should take approximately 15 minutes to complete.

13.7.9 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 non-overlapping 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 and participants who are 18 years old and older will complete it.

13.7.10 Administration Order of Behavioral Rating Scales

The parent and the child can complete the self-administered behavior rating tools in any order.

13.7.11 Checking For Completeness of the Behavioral Rating Scales

A form will be provided to the Study Coordinators to use in making sure that the parent and/or child return all of the self-report surveys prior to receiving their study visit honorarium. It is NOT advised that parents or youth be allowed to take the behavior rating scales home to complete. Each Behavioral Rating forms should be visually scanned after parent's return the form to make sure that all items have been completed. If items have been left blank, the Study Coordinator should encourage the parent and/or child to complete the items to the best of their ability.

13.7.12 English Language Issues

If a parent is not literate, or if written English is difficult for a parent, then it is acceptable to read each item to the respondent using the Reading Assistance Administration Procedures described below, or to use a translator for non-English speaking parents

In the event that the parent speaks Spanish, the CCC will provide Spanish versions of the behavior rating scales if available.

Reading Assistance Administration Procedure - The reading assistant should have a copy of the survey and be seated in a manner that he or she can observe the parent's ability to track items that are being read out loud. The test administrator should read the directions and review the sample questions to assess the respondent's ability to comprehend the response options. The reading assistant should indicate the item number, read the question verbatim, and then ask the respondent to circle the answer of their choice. Care should be taken that the provided reading assistance does not impinge on the respondent's sense of confidentiality.

13.8 QUESTIONS:

Drs. Hooper, Gerson and Johnson are available to answer questions and assist with protocol implementation.

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13.9 EXAMPLES OF TEMPLATES FOR USE IN PROVIDING FEEDBACK TO NEPROLOGISTS

Nephrologist FEEDBACK TEMPLATE: Ages >12 to <30 months

To the Nephrologist of _____:

On [date of neurocognitive evaluation], as a part of [his/her] participation in the Chronic Kidney Disease in Children (CKiD) study, the following tests were administered by [name of psychologist]:

Mullen Scales of Early Learning

Please note that these results were obtained as part of a research study. These results by themselves should not be used to make clinical or educational decisions. A more comprehensive evaluation with a Neuropsychologist is needed to make educational decisions or decisions about mental health needs. A letter describing the test results will be sent to the parent. In keeping with the clinical practice standards of Psychologists the parent feedback will report performance categories (Below Average, Average, Above Average) but not actual test scores. With parental permission the test scores and additional details of the testing results contained in the report below can be released to professionals involved with this child. Feel free to contact the Psychologist listed below if you have questions about this report.

Testing Results:

The Mullen Scales of Early Learning is a comprehensive measure of cognitive function for young children. The test generates five scores (Mean = 50 \pm 10): the Gross Motor Scale and four Cognitive Scales: Visual Reception Scale, Fine Motor Scale, Receptive Language Scale, and Expressive Language Scale. An Early Learning Composite Score (Mean = 100 \pm 15) is computed based on the four Cognitive Scales and serves as a measure of general development/intelligence.

- **Gross Motor** – The items on the Mullen Gross Motor Scale evaluate balance, mobility and motor planning. Gross Motor was in the [Below Average, Average, Above Average] range.
- **Visual Reception** – The items on the Mullen Visual Reception Scale evaluate visual processing skills, spatial organization and visual memory. Visual Reception was in the [Below Average, Average, Above Average] range.
- **Fine Motor** –The items on the Mullen Fine Motor Scale evaluate coordination, visual organization, fine motor planning and fine motor control. Fine Motor was in the [Below Average, Average, Above Average] range.
- **Receptive Language** –The items on the Mullen Receptive Language Scale measure understanding of spoken language, auditory-spatial concepts, memory for commands and general information. Receptive Language was in the [Below Average, Average, Above Average] range.
- **Expressive Language** – The items on the Mullen Expressive Language Scale measure ability to use speech to communicate and express ideas, vocabulary skills, abstract thinking, abstract reasoning, auditory memory and comprehension. Expressive Language was in the [Below Average, Average, Above Average] range.
- **Early Learning Composite** was in the [Below Average, Average, Above Average] range.

	T-Score/Standard Score	Percentile Rank
Gross Motor		
Visual Reception		
Fine Motor		
Receptive Language		
Expressive Language		
Early Learning Composite		

Summary:

(The clinician should feel free to provide a summary paragraph)

Nephrologist FEEDBACK TEMPLATE: Ages 30 months to <4 years

To the Nephrologist of _____:

On [date of neurocognitive evaluation] as a part of his/her participation in the Chronic Kidney Disease in Children (CKiD) study, the following tests were administered by [name of psychologist]:

WPPSI-III (2:6-3:11)

Please note that these results were obtained as part of a research study. These results by themselves should not be used to make clinical or educational decisions. A more comprehensive evaluation with a Neuropsychologist is needed to make educational decisions or decisions about mental health needs. A letter describing the test results will be sent to the parent. In keeping with the clinical practice standards of Psychologists the parent feedback will report performance categories (Below Average, Average, Above Average) but not actual test scores. With parental permission the test scores and additional details of the testing results contained in the report below can be released to professionals involved with this child. Feel free to contact the Psychologist listed below if you have questions about this report.

Testing Results:

This version of the Wechsler Preschool and Primary Scale of the Intelligence – Third Edition (WPPSI-III) was designed for children between the ages of 2 years, 6 months through 3 years, 11 months and includes four core subtests (Mean = 10 ± 3): Receptive Vocabulary, Block Design, Information, and Object Assembly. Composite scores for Verbal IQ, Performance IQ and Full Scale IQ are generated by combining subtest scores (Mean = 100 ± 15).

- **Receptive Vocabulary** – The items on the Receptive Vocabulary Subtest measure a child’s ability to comprehend verbal instructions, auditory and visual discrimination skills, and auditory memory and auditory processing skills. Receptive Vocabulary was in the [Below Average, Average, Above Average] range.
- **Block Design** – The items on the Block Design Subtest measure a child’s ability to analyze abstract visual stimuli, nonverbal concept formation skills, visual perception and organization, and visual-motor coordination. Block Design was in the [Below Average, Average, Above Average] range.
- **Information** – The items on the Information Subtest measure a child’s ability to acquire, retain and retrieve general knowledge. Information was in the [Below Average, Average, Above Average] range.
- **Object Assembly** – The items on the Object Assembly Subtest measure a child’s visual-perceptual organization, skill in integrating and synthesizing part-whole relationships, and nonverbal reasoning ability. Object Assembly was in the [Below Average, Average, Above Average] range.

The WPPSI-III Verbal IQ (VIQ) is based on comprehension, complex language expression, and connected language. VIQ was in the [Below Average, Average, Above Average] range. The WPPSI-III Performance IQ (PIQ) is based on perceptual analysis and manual manipulation of visual and visual-spatial stimuli. The PIQ was in the [Below Average, Average, Above Average] range. Full Scale IQ was in the [Below Average, Average, Above Average] range.

	Scaled Score/Standard Score	Percentile Rank
Receptive Vocabulary		
Block Design		
Information		
Object Assembly		
Verbal IQ		
Performance IQ		
Full Scale IQ		

Summary:

(The clinician should feel free to provide a summary paragraph)

Nephrologist FEEDBACK TEMPLATE: Ages ≥ 4 to < 6 years

To the Nephrologist of _____:

On [date of neurocognitive evaluation] as a part of his/her participation in the Chronic Kidney Disease in Children (CKiD) study, the following tests were administered by [name of psychologist]:

WPPSI-III (4:0-7:3)
K-CPT

Please note that these results were obtained as part of a research study. These results by themselves should not be used to make clinical or educational decisions. A more comprehensive evaluation with a Neuropsychologist is needed to make educational decisions or decisions about mental health needs. A letter describing the test results will be sent to the parent. In keeping with the clinical practice standards of Psychologists the parent feedback will report performance categories (Below Average, Average, Above Average) but not actual test scores. With parental permission the test scores and additional details of the testing results contained in the report below can be released to professionals involved with this child. Feel free to contact the Psychologist listed below if you have questions about this report.

Testing Results

This version of the Wechsler Preschool and Primary Scale of the Intelligence – Third Edition (WPPSI-III) was designed for children between the ages of 4 years through 5 years, 11 months and includes 7 core subtests (Mean = 10 ± 3): Block Design, Information, Matrix Reasoning, Vocabulary, Picture Concepts, Word Reasoning and Coding. Composite scores for Verbal IQ, Performance IQ and Full Scale IQ are generated using subtest scores (Mean = 100 ± 15).

- **Block Design** – The items on the Block Design Subtest measure a child’s ability to analyze abstract visual stimuli, nonverbal concept formation skills, visual perception and organization, visual-motor coordination, and learning ability. Block Design was in the [Below Average, Average, Above Average] range.
- **Information** – The items on the Information Subtest measure a child’s ability to acquire, retain and retrieve general knowledge. Information was in the [Below Average, Average, Above Average] range.
- **Matrix Reasoning** – The items on the Matrix Reasoning Subtest measure a child’s visual information processing skills and abstract reasoning skills. Matrix Reasoning was in the [Below Average, Average, Above Average] range.
- **Vocabulary** – The items on the Vocabulary Subtest measure a child’s verbal knowledge, verbal concept formation skills, long-term memory, and language development. Vocabulary was in the [Below Average, Average, Above Average] range.
- **Picture Concepts** – The items on the Picture Concepts Subtest measure a child’s abstract reasoning ability and categorical reasoning ability. Picture Concepts was in the [Below Average, Average, Above Average] range.
- **Word Reasoning** – The items on the Word Reasoning Subtest measure a child’s verbal comprehension skills, reasoning ability, verbal abstraction skills, domain knowledge, and the ability to generate alternative concepts. Word Reasoning was in the [Below Average, Average, Above Average] range.
- **Coding** – The Coding Subtest measure a child’s short-term memory, learning ability, visual perception, visual-motor coordination, visual scanning ability, cognitive flexibility, attention, and motivation. Coding was in the [Below Average, Average, Above Average] range.

The WPPSI-III Verbal IQ (VIQ) is based on comprehension, complex language expression, and connected language. The VIQ was in the [Below Average, Average, Above Average] range. The WPPSI-III Performance IQ (PIQ) is based on perceptual analysis and manual manipulation of visual and visual-spatial stimuli. The PIQ was in the [Below Average, Average, Above Average] range. The WPPSI-III Full Scale IQ was in the [Below Average, Average, Above Average] range.

	Scaled Score/Standard Score	Percentile Rank
Block Design		
Information		
Matrix Reasoning		
Vocabulary		
Picture Concepts		
Word Reasoning		
Coding		
Verbal IQ		
Performance IQ		
Full-Scale IQ		

This child was asked to complete the Kiddie Conners' Continuous Performance Test (K-CPT) in order to assess attentional functioning. The K-CPT measures the ability to sustain attention as well as the ability to inhibit impulsive responding. The number of Errors of Omissions (paying attention over time) was in the [Below Average, Average, Above Average] range. The number of Errors of Commissions (impulsive responses) was in the [Below Average, Average, Above Average] range.

	T-Score
Errors of Omissions	
Errors of Commissions	

Summary:

(The clinician should feel free to provide a summary paragraph)

Nephrologist FEEDBACK TEMPLATE: Ages ≥ 6 to < 18 years

To the Nephrologist of _____:

On [date of neurocognitive evaluation] as a part of his/her participation in the Chronic Kidney Disease in Children (CKiD) study, the following tests were administered by [name of psychologist]:

WASI-II Vocabulary Subtest and Matrix Reasoning Subtest

CPT-II

Digit Span Forward and Backwards

Spatial Span Forward and Backwards

D-KEFS Subtests (Tower, Verbal Fluency, Design Fluency, Color-Word)

Please note that these results were obtained as part of a research study. These results by themselves should not be used to make clinical or educational decisions. A more comprehensive evaluation with a Neuropsychologist is needed to make educational decisions or decisions about mental health needs. A letter describing the test results will be sent to the parent. In keeping with the clinical practice standards of Psychologists the parent feedback will report performance categories (Below Average, Average, Above Average) but not actual test scores. With parental permission the test scores and additional details of the testing results contained in the report below can be released to professionals involved with this child. Feel free to contact the Psychologist listed below if you have questions about this report.

Testing Results

The Wechsler Abbreviated Scale of Intelligence-II (WASI-II) is a brief and reliable measure of general cognitive functioning. Two subtests were administered during this testing (Mean = 50 ± 10): Vocabulary and Matrix Reasoning. The results from these subtests also produce a Full Scale IQ (Mean = 100 ± 15).

- **Vocabulary** – The WASI-II Vocabulary Subtest evaluates a child’s verbal knowledge, verbal concept formation, learning ability, long-term memory, and language development. Vocabulary was in the [Below Average, Average, Above Average] range.
- **Matrix Reasoning** – The WASI-II Matrix Reasoning Subtest evaluates a child’s visual information processing and abstract reasoning skills. Matrix Reasoning was in the [Below Average, Average, Above Average] range.

The WASI-II Full Scale IQ was in the [Below Average, Average, Above Average] range.

	T-Score/Standard Score	Percentile Rank
Vocabulary		
Matrix reasoning		
Full-2 IQ		

This child was asked to complete the **Conners’ Continuous Performance Test (CPT-II)** to assess ability to sustain attention and inhibit impulsive responding. The number of Errors of Omissions (paying attention over time) was in the [Below Average, Average, Above Average] range. The number of Errors of Commissions (impulsive responses) was in the [Below Average, Average, Above Average] range.

	T-Score
Errors of Omissions	
Errors of Commissions	

This child was asked to complete a Wechsler **Digit Span Subtest**. Digit Span Forward provides an estimate of attention and short-term verbal memory. Digit Span Backward provides an estimate of verbal working memory. Digit Span Forward was in the [Below Average, Average, Above Average] range, Digit Span Backward was in the [Below Average range, Average, Above Average] range.

This child was asked to complete a Wechsler **Spatial Span Subtest**. Spatial Span Forward provides an estimate of attention and short-term visual memory. Spatial Span Backward provides an estimate of visual working memory. Spatial Span Forward was in the [Below Average, Average, Above Average] range. Spatial Span Backward was in the [Below Average, Average, Above Average] range.

The table below contains scaled scores (mean = 10 ±3) for Digit Span and Spatial Span tasks.

	Scaled Score
Wechsler Digit Span	
Forward	
Backward	
Wechsler Spatial Span	
Forward	
Backward	

This child was asked to complete several subtests of the Delis-Kaplan Executive Function System (D-KEFS)

- The **Tower** task provides an estimate of overall planning and problem solving. D-KEFS Tower task was in the [Below Average, Average, Above Average] range.
- The **Verbal Fluency** task provides an estimate of verbal efficiency. D-KEFS Verbal Fluency task was in the [Below Average, Average, Above Average] range.
- The **Design Fluency** task provides an estimate of nonverbal efficiency. D-KEFS Design Fluency task was in the [Below Average, Average, Above Average] range.
- The **Color-Word Interference** task provides an estimate of set-shifting and inhibitory control. D-KEFS Color-Word Interference task was in the [Below Average, Average, Above Average] range.

Specific scaled scores for the D-KEFS tasks are listed below (scaled score mean = 10 ± 3).

	Scaled Score
Tower Total Achievement	
Verbal Fluency	
FAS Letter	
Category Fluency	
Category Switching	
Category Switching Total Switching	
Design Fluency Total	
Color-Word Interference	
Inhibition	
Inhibition Switching	

Summary:

(The clinician should feel free to provide a summary paragraph)

Nephrologist FEEDBACK TEMPLATE: Ages \geq 18 years

To the Nephrologist of _____:

On [date of neurocognitive evaluation] as a part of his/her participation in the Chronic Kidney Disease in Children (CKiD) study, the following tests were administered by [name of psychologist]:

Wechsler Abbreviated Scale of Intelligence-II (WASI-II) Vocabulary Subtest and Matrix Reasoning Subtest
Conners' Continuous Performance Test (CPT-II)
Wechsler Digit Span Forward and Backward
Wechsler Spatial Span Forward and Backward
D-KEFS Subtests (Tower, Verbal Fluency, Design Fluency, Color-Word Interference)

Please note that these results were obtained as part of a research study. These results by themselves should not be used to make clinical or educational decisions. A more comprehensive evaluation with a Neuropsychologist is needed to make educational decisions or decisions about mental health needs. A letter describing the test results will be sent to the parent. In keeping with the clinical practice standards of Psychologists the parent feedback will report performance categories (Below Average, Average, Above Average) but not actual test scores. With parental permission the test scores and additional details of the testing results contained in the report below can be released to professionals involved with this child. Feel free to contact the Psychologist listed below if you have questions about this report.

Testing Results:

The Wechsler Abbreviated Scale of Intelligence-II (WASI-II) is a brief and reliable measure of general cognitive functioning. Two subtests were administered during this testing (Mean = 50 ± 10): Matrix Reasoning and Vocabulary. The results from these subtests produce a Full Scale IQ (Mean = 100 ± 15).

- **Vocabulary** – The WASI-II Vocabulary Subtest evaluates verbal knowledge, verbal concept formation, learning ability, long-term memory, and language development. Vocabulary was in the [Below Average, Average, Above Average] range.
- **Matrix Reasoning** – The WASI-II Matrix Reasoning Subtest evaluates visual information processing and abstract reasoning skills. Matrix Reasoning was in the [Below Average, Average, Above Average] range.

The WASI-II Full Scale IQ was in the [Below Average, Average, Above Average] range.

	T-Score/Standard Score	Percentile Rank
Vocabulary		
Matrix reasoning		
Full Scale IQ		

This participant was asked to complete the **Conners' Continuous Performance Test (CPT-II)** to assess ability to sustain attention and inhibit impulsive responding over time. The number of Errors of Omissions (paying attention over time) was in the [Below Average, Average, Above Average] range. The number of Errors of Commissions (impulsive responses) was in the [Below Average, Average, Above Average] range.

	T-Score
Errors of Omissions	
Errors of Commissions	

This participant was asked to complete a Wechsler **Digit Span Subtest**. Digit Span Forward provides an estimate of attention and short-term verbal memory. Digit Span Backward provides an estimate of verbal working memory. Digit Span Forward was in the [Below Average, Average, Above Average] range. Digit Span Backward was in the [Below Average, Average, Above Average] range.

This participant was asked to complete a Wechsler **Spatial Span Subtest** (Mean = 10 ± 3). Spatial Span Forward provides an estimate of attention and short-term visual memory. Spatial Span Backward provides an estimate of

visual working memory. Spatial Span Forward was in the [Below Average, Average, Above Average] range. Spatial Span Backward was in the [Below Average, Average, Above Average] range.

	Scaled Score
Wechsler Digit Span	
Forward	
Backward	
Wechsler Spatial Span	
Forward	
Backward	

This participant was asked to complete several subtests (Mean = 10 ± 3) of the Delis-Kaplan Executive Function System (D-KEFS). These tasks provide estimates for several aspects of executive functioning.

- The **Tower** task provides an estimate of overall planning and problem solving. D-KEFS Tower task was in the [Below Average, Average, Above Average] range.
- The **Verbal Fluency** task provides an estimate of verbal efficiency. D-KEFS Verbal Fluency task was in the [Below Average, Average, Above Average] range.
- The **Design Fluency** task provides an estimate of nonverbal efficiency. D-KEFS Design Fluency task was in the [Below Average, Average, Above Average] range.
- The **Color-Word Interference** task provides an estimate of set-shifting and inhibitory control. D-KEFS Color-Word Interference task was in the [Below Average, Average, Above Average] range.

	Scaled Score
Tower Total Achievement	
Verbal Fluency	
FAS	
Category Fluency	
Category Switching	
Category Switching Total Switching	
Design Fluency Total	
Color-Word Interference	
Inhibition	
Inhibition Switching	

Summary:

(The clinician should feel free to provide a summary paragraph)

13.10 EXAMPLE OF TEMPLATE FOR USE IN PROVIDING FEEDBACK TO YOUNG ADULTS

YOUNG ADULT FEEDBACK TEMPLATE: For young adults Ages >18 years

Dear _____,

On [date of neurocognitive evaluation], as a part of your participation in the Chronic Kidney Disease in Children (CKiD) study, the following tests were administered to you by [psychologist name]:

WASI-II Vocabulary Subtest and Matrix Reasoning Subtest
CPT-II
Wechsler Digit Span Forward and Backward
Wechsler Spatial Span Forward and Backward
D-KEFS Subtests (Tower, Verbal Fluency, Design Fluency, Color-Word Interference)

Please remember that these results were obtained as part of a research study, not as part of a routine visit with a psychologist. You should not use these results by themselves to make clinical or educational decisions. A more in-depth visit with a psychologist is needed if at any time you need to make educational decisions, or if you need mental health treatment. Please contact the Psychologist listed below if you have any questions about these test results. A letter describing the test results will be sent to your Nephrologist.

Testing Results:

The Wechsler Abbreviated Scale of Intelligence-II (WASI-II) is a brief and reliable measure of general cognitive functioning. Two subtests were administered during this testing: Vocabulary and Matrix Reasoning. The results from these subtests produce a two-subtest Full Scale IQ.

- **Vocabulary** – The WASI-II Vocabulary Subtest evaluates ~~a child's~~ verbal knowledge, verbal concept formation, learning ability, long-term memory, and language development. Vocabulary was in the [Below Average, Average, Above Average] range.
- **Matrix Reasoning** – The WASI-II Matrix Reasoning Subtest evaluates ~~a child's~~ visual information processing and abstract reasoning skills. Matrix Reasoning was in the [Below Average, Average, Above Average] range.

The WASI-II Full Scale IQ score was in the [Below Average, Average, Above Average] range.

You were asked to complete the **Conners' Continuous Performance Test (CPT-II)** in order to assess your ability to pay attention over time, and inhibit (or stop) impulsive responding (in other words, to not hit a button when instructed not to do so). The number of Errors of Omissions (paying attention over time) was in the [Below Average, Average, Above Average] range. The number of Errors of Commissions (impulsive responses) was in the [Below Average, Average, Above Average] range.

You were asked to complete a Wechsler **Digit Span Subtest**. Digit Span Forward provides an estimate of attention and short-term verbal memory. Digit Span Backward provides an estimate of verbal working memory. The Digit Span Forward score was in the [Below Average, Average, Above Average] range. The Digit Span Backward score was in the [Below Average range, Average, Above Average] range.

You were asked to complete a Wechsler **Spatial Span Subtest**. Spatial Span Forward provides an estimate of attention and short-term visual memory. Spatial Span Backward provides an estimate of visual working memory. The Spatial Span Forward was in the [Below Average, Average, Above Average] range. The Spatial Span Backward was in the [Below Average, Average, Above Average] range.

You were asked to complete several subtests of the Delis-Kaplan **Executive Function System (D-KEFS)**. These tasks provide estimates for several aspects of executive functioning.

- The **Tower** task provides an estimate of overall planning and problem solving. D-KEFS Tower task was in the [Below Average, Average, Above Average] range.
- The **Verbal Fluency** task provides an estimate of verbal efficiency. D-KEFS Verbal Fluency task was in the [Below Average, Average, Above Average] range.
- The **Design Fluency** task provides an estimate of nonverbal efficiency. D-KEFS Design Fluency task was in the [Below Average, Average, Above Average] range.
- The **Color-Word Interference** task provides an estimate of set-shifting and inhibitory control. D-KEFS Color-Word Interference task was in the [Below Average, Average, Above Average] range.

Summary:

(The clinician should feel free to provide a summary paragraph)

13.11 EXAMPLE OF TEMPLATE FOR USE IN PROVIDING FEEDBACK TO PARENTS

PARENT FEEDBACK TEMPLATE: Ages ≥ 12 to < 30 months

To the Parent/Guardian(s) of _____:

On [date of neurocognitive evaluation], as a part of [his/her] participation in the Chronic Kidney Disease in Children (CKiD) study, the Mullen Scales of Early Learning was administered by [name of psychologist].

Please remember that these results were obtained as part of a research study, not as part of a routine visit with a psychologist. You should not use these results by themselves to make clinical or educational decisions about your child. A more in-depth visit with a psychologist is needed if at any time you need to make educational decisions about your child, or if your child needs mental health treatment. Please contact the Psychologist listed below if you have any questions about these test results. A letter describing the test results will be sent to your Nephrologist.

Testing Results:

The Mullen Scales of Early Learning is a comprehensive measure of cognitive function for young children. The test generates five scores: the Gross Motor Scale and four Cognitive Scales: Visual Reception Scale, Fine Motor Scale, Receptive Language Scale, and Expressive Language Scale. An Early Learning Composite Score is computed based on the four Cognitive Scales and serves as a measure of general development/intelligence.

- **Gross Motor** – The items on the Mullen Gross Motor Scale evaluate balance, mobility and motor planning. Your child's Gross Motor skills were within the [Below Average, Average, Above Average] range.
- **Visual Reception** – The items on the Mullen Visual Reception Scale evaluate a child's visual processing skills, spatial organization and visual memory. Visual reception was in the [Below Average, Average, Above Average] range.
- **Fine Motor** – The items on the Mullen Fine Motor Scale evaluate a child's coordination, visual organization, fine motor planning and fine motor control. Fine motor skills were within the [Below Average, Average, Above Average] range.
- **Receptive Language** – The items on the Mullen Receptive Language Scale measure a child's understanding of spoken language, auditory-spatial concepts, memory for commands and general information. Receptive language was in the [Below Average, Average, Above Average] range.
- **Expressive Language** – The items on the Mullen Expressive Language Scale measure a child's ability to use speech to communicate and express ideas, and a child's vocabulary skills, abstract thinking, abstract reasoning, auditory memory and comprehension. Expressive language was in the [Below Average, Average, Above Average] range.
- **Early Learning Composite** was in the [Below Average, Average, Above Average] range.

Summary:

(The clinician should feel free to provide a summary paragraph)

PARENT FEEDBACK TEMPLATE: Ages \geq 30 months to <4 years

To the Parent/Guardian(s) of _____:

On [date of neurocognitive evaluation] as a part of his/her participation in the Chronic Kidney Disease in Children (CKiD) study, the following tests were administered by [name of psychologist]:

WPPSI-III (2:6-3:11)

Please remember that these results were obtained as part of a research study, not as part of a routine visit with a psychologist. You should not use these results by themselves to make clinical or educational decisions about your child. A more in-depth visit with a psychologist is needed if at any time you need to make educational decisions about your child, or if your child needs mental health treatment. Please contact the Psychologist listed below if you have any questions about these test results. A letter describing the test results will be sent to your Nephrologist.

Testing Results:

This version of the Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III) was designed for children between the ages of 2 years, 6 months and 3 years, 11 months and includes four core subtest scores: Receptive Vocabulary, Block Design, Information, and Object Assembly. Composite scores for Verbal IQ, Performance IQ and Full Scale IQ are derived by combining scores from the subtests.

- **Receptive Vocabulary** – The items on the Receptive Vocabulary Subtest measure a child's ability to comprehend verbal instructions, auditory and visual discrimination skills, and auditory memory and auditory processing skills. Receptive Vocabulary was in the [Below Average, Average, Above Average] range.
- **Block Design** – The items on the Block Design Subtest measure a child's ability to analyze abstract visual stimuli, nonverbal concept formation skills, visual perception and organization, visual-motor coordination and learning ability. Block Design was in the [Below Average, Average, Above Average] range.
- **Information** – The items on the Information Subtest measure a child's ability to acquire, retain and retrieve general knowledge. Information was in the [Below Average, Average, Above Average] range.
- **Object Assembly** – The items on the Object Assembly Subtest measure a child's visual-perceptual organization, skill in integrating and synthesizing part-whole relationships, and nonverbal reasoning ability. Object Assembly was in the [Below Average, Average, Above Average] range.

The WPPSI-III Verbal IQ (VIQ) is based on comprehension, complex language expression, and connected language. VIQ was in the [Below Average, Average, Above Average] range. The WPPSI-III Performance IQ (PIQ) is based on perceptual analysis and manual manipulation of visual and visual-spatial stimuli. PIQ in the [Below Average, Average, Above Average] range. Your child's Full Scale IQ was in the [Below Average, Average, Above Average] range.

Summary:

(The clinician should feel free to provide a summary paragraph)

PARENT FEEDBACK TEMPLATE: Ages ≥ 4 to < 6 years

To the Parent/Guardian(s) of _____:

On [date of neurocognitive evaluation] as a part of his/her participation in the Chronic Kidney Disease in Children (CKiD) study, the following tests were administered by [name of psychologist]:

WPPSI-III (4:0-7:3)
K-CPT

Please remember that these results were obtained as part of a research study, not as part of a routine visit with a psychologist. You should not use these results by themselves to make clinical or educational decisions about your child. A more in-depth visit with a psychologist is needed if at any time you need to make educational decisions about your child, or if your child needs mental health treatment. Please contact the Psychologist listed below if you have any questions about these test results. A letter describing the test results will be sent to your Nephrologist.

Testing Results:

This version of the Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III) was designed for children between the ages of 4 years and 5 years, 11 months and includes 7 core subtests: Block Design, Information, Matrix Reasoning, Vocabulary, Picture Concepts, Word Reasoning, and Coding. The WPPSI-III provides a measurement of your child's intellectual functioning.

- **Block Design** – The items on the Block Design Subtest measure a child's ability to analyze abstract visual stimuli, nonverbal concept formation skills, visual perception and organization, visual-motor coordination, and learning ability. Block Design was in the [Below Average, Average, Above Average] range.
- **Information** – The items on the Information Subtest measure a child's ability to acquire, retain and retrieve general knowledge. Information was in the [Below Average, Average, Above Average] range.
- **Matrix Reasoning** – The items on the Matrix Reasoning Subtest measure a child's visual information processing skills and abstract reasoning skills. Matrix Reasoning was in the [Below Average, Average, Above Average] range.
- **Vocabulary** – The items on the Vocabulary Subtest measure a child's verbal knowledge, verbal concept formation skills, learning ability, long-term memory, and language development. Vocabulary was in the [Below Average, Average, Above Average] range.
- **Picture Concepts** – The items on the Picture Concepts Subtest measure a child's abstract reasoning ability and categorical reasoning ability. Picture Concepts was in the [Below Average, Average, Above Average] range.
- **Word Reasoning** – The items on the Word Reasoning Subtest measure a child's verbal comprehension skills, reasoning ability, verbal abstraction skills, domain knowledge, and the ability to generate alternative concepts. Word Reasoning was in the [Below Average, Average, Above Average] range.
- **Coding** – The items on the Coding Subtest measure a child's short-term memory, learning ability, visual perception, visual-motor coordination, visual scanning ability,

cognitive flexibility, attention, and motivation. Coding was in the [Below Average, Average, Above Average] range.

The WPPSI-III Verbal IQ (VIQ) is based on comprehension, complex expression, and connected language. The VIQ score was in the [Below Average, Average, Above Average] range. The WPPSI-III Performance IQ (PIQ) is based on perceptual analysis and manual manipulation of visual and visual-spatial stimuli. The PIQ score was in the [Below Average, Average, Above Average] range. Your child's combined index of the WPPSI-III Full Scale IQ was in the [Below Average, Average, Above Average] range.

Your child was asked to complete the Kiddie Conners' Kiddie Continuous Performance Test (K-CPT) in order to assess his/her ability to pay attention over time, and stop his/herself from hitting a button when he/she is told not to. The number of Errors of Omissions (paying attention over time) was in the [Below Average, Average, Above Average] range. The number of Errors of Commissions (impulsive responses) was in the [Below Average, Average, Above Average] range.

Summary:

(The clinician should feel free to provide a summary paragraph)

PARENT FEEDBACK TEMPLATE: Ages ≥ 6 to < 18 years

To the Parent/Guardian(s) of _____:

On [date of neurocognitive evaluation] as a part of his/her participation in the Chronic Kidney Disease in Children (CKiD) study, the following tests were administered by [name of psychologist]:

WASI-II Vocabulary Subtest and Matrix Reasoning Subtest
CPT-II

Wechsler Digit Span Forward and Backward

Wechsler Spatial Span Forward and Backward

D-KEFS Subtests (Tower, Verbal Fluency, Design Fluency, Color-Word Interference)

Please remember that these results were obtained as part of a research study, not as part of a routine visit with a psychologist. You should not use these results by themselves to make clinical or educational decisions about your child. A more in-depth visit with a psychologist is needed if at any time you need to make educational decisions about your child, or if your child needs mental health treatment. Please contact the Psychologist listed below if you have any questions about these test results. A letter describing the test results will be sent to your Nephrologist.

Testing Results:

The Wechsler Abbreviated Scale of Intelligence-II (WASI-II) is a brief and reliable measure of general cognitive functioning. Two subtests were administered during this testing: Vocabulary and Matrix Reasoning. The results from these subtests produce a two-subtest Full Scale IQ.

- **Vocabulary** – The WASI-II Vocabulary Subtest evaluates a child’s verbal knowledge, verbal concept formation, learning ability, long-term memory, and language development. Vocabulary was in the [Below Average, Average, Above Average] range.
- **Matrix Reasoning** – The WASI-II Matrix Reasoning Subtest evaluates a child’s visual information processing and abstract reasoning skills. Matrix Reasoning was in the [Below Average, Average, Above Average] range.

The WASI-II Full Scale IQ score was in the [Below Average, Average, Above Average] range.

Your child was asked to complete the **Conners’ Continuous Performance Test (CPT-II)** in order to assess his/her ability to pay attention over time, and inhibit (or stop) impulsive responding (in other words, to not hit a button when instructed not to do so). The number of Errors of Omissions (paying attention over time) was in the [Below Average, Average, Above Average] range. The number of Errors of Commissions (impulsive responses) was in the [Below Average, Average, Above Average] range.

Your child was asked to complete a Wechsler **Digit Span Subtest**. Digit Span Forward provides an estimate of attention and short-term verbal memory. Digit Span Backward provides an estimate of verbal working memory. The Digit Span Forward score was in the [Below Average, Average, Above Average] range. The Digit Span Backward score was in the [Below Average, Average, Above Average] range.

Your child was asked to complete a Wechsler **Spatial Span Subtest**. Spatial Span Forward provides an estimate of attention and short-term visual memory. Spatial Span Backward provides an estimate of visual working memory. The Spatial Span Forward was in the [Below

Average, Average, Above Average] range. The Spatial Span Backward was in the [Below Average, Average, Above Average] range.

Your child was asked to complete several subtests of the Delis-Kaplan **Executive Function System (D-KEFS)**. These tasks provide estimates for several aspects of executive functioning.

- The **Tower** task provides an estimate of overall planning and problem solving. D-KEFS Tower task was in the [Below Average, Average, Above Average] range.
- The **Verbal Fluency** task provides an estimate of verbal efficiency. D-KEFS Verbal Fluency task was in the [Below Average, Average, Above Average] range.
- The **Design Fluency** task provides an estimate of nonverbal efficiency. D-KEFS Design Fluency task was in the [Below Average, Average, Above Average] range.
- The **Color-Word Interference** task provides an estimate of set-shifting and inhibitory control. D-KEFS Color-Word Interference task was in the [Below Average, Average, Above Average] range.

Summary:

(The clinician should feel free to provide a summary paragraph)

APPENDIX A. Reliability Recording Coding Worksheet (version 03/01/14)

CKID Neurocognitive Protocol Reliability Recording Worksheet: KID# _____, Date of Testing _____

	Primary Reliability Code	Secondary Reliability Code
NOTE: This should be completed and transcribed to the appropriate Cognitive-Developmental Data Coding Sheet.	1 – Standard procedure, Reliable Results 2 – Irregular Procedure, Reliability Impact Minor (e.g., child tired, but able to complete task) 3 – Irregular Procedure, Unreliable (e.g., child too active, too ill; too tired, examiner errors) 4 – Participant Attempted – Participant too Impaired to Complete 5 – Participant Attempted - Examiner Discontinued 6 – Participant Attempted - Refused to Finish 7 – Participant Refused to Begin 8 – Not attempted - Reason UNRELATED to Participant (e.g., examiner forgot, procedure not available)	.0 – Use this secondary reliability code when standard procedure with adequate reliability OR irregular procedure with adequate reliability occurred. or .0 – Testing problem not directly related to the patient (e.g., trained examiner not available, improper test administration, procedure not available). .1 – Testing problems primarily related to physical limitations, injuries or disabilities of the participant (not cognitive in nature) .2 – Testing problems primarily related to cognitive deficits or impairments in cognition, and/or behaviors of the participant.
MULLEN		
Gross Motor	1 2 3 4 5 6 7 8	.0 .1 .2
Visual Reception	1 2 3 4 5 6 7 8	.0 .1 .2
Fine-Motor	1 2 3 4 5 6 7 8	.0 .1 .2
Receptive Language	1 2 3 4 5 6 7 8	.0 .1 .2
Expressive Language	1 2 3 4 5 6 7 8	.0 .1 .2
Early Learning Composite		
WPPSI-III (younger)	Primary Reliability Code	Secondary Reliability Codes
Receptive Vocabulary	1 2 3 4 5 6 7 8	.0 .1 .2
Block Design	1 2 3 4 5 6 7 8	.0 .1 .2
Information	1 2 3 4 5 6 7 8	.0 .1 .2
Object Assembly	1 2 3 4 5 6 7 8	.0 .1 .2
WPPSI-III (older)	Primary Reliability Code	Secondary Reliability Codes
Block Design	1 2 3 4 5 6 7 8	.0 .1 .2
Information	1 2 3 4 5 6 7 8	.0 .1 .2
Matrix Reasoning	1 2 3 4 5 6 7 8	.0 .1 .2
Vocabulary	1 2 3 4 5 6 7 8	.0 .1 .2
Picture Concepts	1 2 3 4 5 6 7 8	.0 .1 .2
Word Reasoning	1 2 3 4 5 6 7 8	.0 .1 .2
Coding	1 2 3 4 5 6 7 8	.0 .1 .2
K-CPT	Primary Reliability Code	Secondary Reliability Codes
Overall Reliability	1 2 3 4 5 6 7 8	.0 .1 .2

CKID Neurocognitive Protocol Reliability Recording Worksheet: KID #: _____ Date of Testing: _____

	Primary Reliability Code	Secondary Reliability Code
	1 – Standard procedure, Reliable Results 2 – Irregular Procedure, Reliability Impact Minor (e.g., child tired, but able to complete task) 3 – Irregular Procedure, Unreliable (e.g., child too active, too ill; too tired, examiner errors) 4 – Participant Attempted – Participant too Impaired to Complete 5 – Participant Attempted - Examiner Discontinued 6 – Participant Attempted - Refused to Finish 7 – Participant Refused to Begin 8 – Not attempted - Reason UNRELATED to Participant (e.g., examiner forgot, procedure not available)	.0 – Use this secondary reliability code when standard procedure with adequate reliability OR irregular procedure with adequate reliability occurred. or .0 – Testing problem not directly related to the patient (e.g., trained examiner not available, improper test administration, procedure not available). .1 - Testing problems primarily related to physical limitations, injuries or disabilities of the participant (not cognitive in nature). .2 – Testing problems primarily related to cognitive deficit: impairments in cognition, and/or behaviors of the participant
WASI II		
Vocabulary	1 2 3 4 5 6 7 8	.0 .1 .2
Matrix reasoning	1 2 3 4 5 6 7 8	.0 .1 .2
CPT-II	Primary Reliability Code	Secondary Reliability Codes
Overall Reliability	1 2 3 4 5 6 7 8	.0 .1 .2
WISC-IV DIGIT SPAN OR WAIS-IV DIGIT SPAN	Primary Reliability Code	Secondary Reliability Codes
Digit Span Forward	1 2 3 4 5 6 7 8	.0 .1 .2
Digit Span Backward	1 2 3 4 5 6 7 8	.0 .1 .2
WISC-IV Integrated OR WMS-III	Primary Reliability Code	Secondary Reliability Codes
Spatial Span Forward	1 2 3 4 5 6 7 8	.0 .1 .2
Spatial Span Backward	1 2 3 4 5 6 7 8	.0 .1 .2
D-KEFS Subtests	Primary Reliability Code	Secondary Reliability Codes
Tower	1 2 3 4 5 6 7 8	.0 .1 .2
Verbal Fluency: FAS Letter Fluency	1 2 3 4 5 6 7 8	.0 .1 .2
Verbal Fluency: Category Fluency	1 2 3 4 5 6 7 8	.0 .1 .2
Verbal Fluency: Category Switching	1 2 3 4 5 6 7 8	.0 .1 .2
Design Fluency: Fill Dots	1 2 3 4 5 6 7 8	.0 .1 .2
Design Fluency: Empty Dots	1 2 3 4 5 6 7 8	.0 .1 .2
Design Fluency: Switching	1 2 3 4 5 6 7 8	.0 .1 .2
Color-Word Interference: Color Naming	1 2 3 4 5 6 7 8	.0 .1 .2
Color-Word Interference: Word Reading	1 2 3 4 5 6 7 8	.0 .1 .2
Color-Word Interference: Inhibition	1 2 3 4 5 6 7 8	.0 .1 .2
Color-Word Interference: Inhibition/Switching	1 2 3 4 5 6 7 8	.0 .1 .2

BEHAVIORAL ALERT ITEMS

Directions: Please review the age appropriate BASC-2 PRS form for the ALERT ITEMS listed below. On the BASC-2, if the parent selected sometimes (S), often (O), or always (A) to any of the items, place an "X" in the box provided.

CHECK ENDORSED ITEMS:

A.	<input type="checkbox"/>	BASC-2 PRS Ages 2-5	127. Sets Fires
B.	<input type="checkbox"/>	BASC-2 PRS Ages 6-11	92. Says, "I want to die", or "I wish I were dead"
C.	<input type="checkbox"/>	BASC PRS Ages 6-11	97. Is cruel to animals
D.	<input type="checkbox"/>	BASC PRS Ages 6-11	138. Says, "I want to kill myself"
E.	<input type="checkbox"/>	BASC PRS Ages 6-11	143. Sets Fires
F.	<input type="checkbox"/>	BASC PRS Ages 12-21	25. Is cruel to animals
G.	<input type="checkbox"/>	BASC PRS Ages 12-21	40. Threatens to hurt others
H.	<input type="checkbox"/>	BASC PRS Ages 12-21	60. Says, "I want to kill myself"
I.	<input type="checkbox"/>	BASC PRS Ages 12-21	90. Says, "I want to die", or "I wish I were dead"
J.	<input type="checkbox"/>	BASC PRS Ages 12-21	121. Sets Fires
		BASC-SRP Ages 18-25	Does not contain any behavioral alert items.
<input type="checkbox"/> NONE of the items were endorsed by child and/or parent: If Items (A-J) were NOT endorsed, please enclose this form along with the other study forms and mail to the CCC.			

If ANY of the items (A-J) were endorsed, please complete the following questions and then email or fax this form to your Clinical Coordinating Center (CCC) within 48 hours of the study visit.

1. Indicate the actions taken at your site as a result of the alert (respond "Yes" or "No" for sub-questions a-c):
 - a. The nephrologist or CKID principal investigator was contacted: Yes No
 - i. Name of physician contacted: _____
 - ii. Date of contact: ____/____/____
 - iii. Initials of staff who made contact: ____
 - b. The family/subject was queried about the behavioral alert items at the time of the visit: Yes No
 - c. The family/subject was contacted after the CKiD visit: Yes No
 - d. Please briefly describe the plan that was generated by your team in response to the behavioral alert:

Please send your completed form to:

East Coast Clinical Sites:

Jackie Ndirangu, Project Director
 Phone: (267)-426-8388
 Email: NdiranguJ@email.chop.edu
 Fax: (267)-426-8113

Midwest Clinical Sites:

Julie Starr, Project Director
 Phone: (816)-855-1744
 Email: jwstarr@cmh.edu
 Fax: (816)-302-9919

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 14: NEUROIMAGING

14.1 OVERVIEW

This section describes the neuroimaging procedures and the additional neuropsychological procedures that will be used in the sub-cohort at up to three clinical sites. We will collect both functional (fMRI) and structural (MRI, DTI) on 60 children and adolescents of which approximately 15 participants will be part of the CKiD Study. This design was chosen, in part, to ascertain a typical group and a more severely involved group for comparison purposes.

DELETED Additional Neuropsychological measures for high risk children from protocol

14.4 DESCRIPTION OF NEUROIMAGING PILOT

The British Columbia Children's Hospital site's recruitment goal is approximately 30 child/adolescent cases on their 1.5 T scanner which includes 10 mild cases of CKD (overlap with CKiD study participants), 10 controls, and 10 severe/ESRD/dialysis/transplant cases. The University of North Carolina (UNC) site has similar goals for ascertainment, but will use a 3.0 T scanner. Together, the two sites will have approximately 60 cases ranging across severity: Controls (n = 20), Mild/Moderate CKD (n = 20), and Severe/ESRD/Dialysis/Transplant (n = 20). In addition, cases from one other CKiD clinical site may also be added to the dataset. Each site will collect structural MRI, DTI, and fMRI.

Inclusion criteria for this portion of the CKiD study are:

- Ages 9–19 years
- Mild/Moderate CKD
- Severe/ESRD, Dialysis Dependent, or Post-Transplant
- Healthy Controls

Exclusion criteria for this portion of the CKiD Study are:

- Hospitalization within 1 week of scan
- Presence of acute illness
- The presence of claustrophobia
- Permanent metal devices in the body
- Currently pregnant or breastfeeding

History of traumatic brain injury

14.4.1 Neuroimaging Protocol

For the structural brain data, the acquisition sequence was determined to facilitate the development of both volumetric data as well as diffusion tensor imaging data:

- T1 weighted sequence (1x1x1 isotropic resolution): 3D IR-Prepped FSPGR, TE: Min Fill, TR: Minimum, Prep Time: 450, Flip Angle: 12, Bandwidth: 15.63, 256x192, NEX: 1, FOV: 25.6, slice Thickness: 1mm, 160 slices, Scan Time w/asset = 3:55.
- T2 weighted sequence (1x1x1 isotropic resolution): 2D Fast Spin Echo, TE: 85 ms, TR: 3000, ETL: 8, BW: 15.63, 256X192, NEX: 1, FOV: 25.6, Slice Thickness: 1, 160 slices, Scan Time w/ asset = 4:55 (Note: adding a PD within the T2 sequence will increase the scan time to 9:07).
- DTI (2x2x2 isotropic resolution): 15 directions, TR: 17000, FOV: 25.6, Slice Thickness: 2, 80 slices, Scan time w/asset = 5:06.
- The T1 and T2 sequences are both isotropic 1x1x1 mm voxels. This would allow for reorientation for any volumetric measurements without any serious interpolation problems. The structural scans will require study participants to remain still during the scanning series.

For the functional brain imaging (fMRI), the following sequence will be used at both sites:

- 3T MRI
- Functional images acquired during task using gradient-echo EPI (24 oblique slices, 3.75 mm, FOV 24 cm; TE: 30 ms; TR: 1500 ms; flip angle 80)

The functional scans will be conducted while the participants are engaged in a Visual-Spatial Working Memory Task. This task will require the participant to determine the location of 1 green square to 1 of 4 previously presented red squares. The task will produce findings related to brain activity during the encoding and delay components of the task. There will be 1 session per subject, with 4 runs of the task where each run will include 10 trials.

14.4.2. Neuroimaging data storage and distribution

Data will be stored at Vancouver and University of North Carolina. UNC will store and analyze fMRI and Vancouver will be responsible for the storage and analysis of the structural data.

14.5 QUESTIONS

All questions regarding the neurocognitive battery should be addressed to:

Stephen R. Hooper, Ph.D.

Professor and Clinical Neuropsychologist

Clinical Center for the Study of Development and Learning, Campus Box # 7255

University of North Carolina School of Medicine

Chapel Hill, NC 27599-7255

Telephone: 919-966-5171

Fax: 919-966-2230

E-mail: stephen.hooper@cdl.unc.edu.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 15: NUTRITIONAL ASSESSMENT

15.1 OVERVIEW

This section describes the procedures to obtain a nutritional assessment. The nutritional assessment consists of:

- I. Food Frequency Questionnaire (FFQ)
- II. Emesis and Diarrhea – Symptoms List
- III. Appetite Rating – Medical History Form and F15 (Nutritional Assessment)
- IV. Gastrostomy or NG Tube – F15 (Nutritional Assessment)
- V. Nutritional supplements – F15 (Nutritional Assessments)

15.2 FOOD FREQUENCY QUESTIONNAIRE

Food Frequency Questionnaire will be completed on a yearly basis beginning at the second baseline visit (V1b). During the study visit, the parents and/or child should be instructed to complete the age appropriate FFQ and return the completed form to the clinical site study coordinator. When the family returns the FFQ to the study coordinator, he/she must review the forms for completeness. If missing information, the study coordinator should attempt clarification with family and send 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.

15.2.1 Specific Instructions for Clinical Coordinating Centers

The CCCs should batch and ship the FFQs to the Data Coordinating Center (DCC).

The FFQs should be batched and sent to:

KIDMAC
Bloomberg School of Public Health
Johns Hopkins University
615 N. Wolfe Street, E7007
Baltimore, MD 21205
Phone: (410) 614-1277
E-mail: jjerry@jhu.edu

After the majority of batched forms are received, the DCC will send the FFQs to the Harvard School of Public Health for analysis. The analysis will include a nutrient analysis, a contribution file (top ten foods on the FFQ contributing to each nutrient) and an average serving of food.

15.3 EMESIS AND DIARRHEA

The family should be asked regarding the frequency of these problems, on average, over the last month, and rate the severity of symptoms (mild, moderate, or severe).

15.4 APPETITE RATING

This question should be asked of the primary caregiver. The same person should, if possible, answer this question each year.

15.5 GASTROSTOMY OR NG TUBE

The family should be asked regarding the **use** of a gastrostomy or NG tube for nutrition (use for medications only or the presence of a tube that is not being used is not counted). If the family answers yes, then record the number of months of use (out of the last 12) for nutritional support.

15.6 NUTRITIONAL SUPPLEMENTS

The family should also be asked what, if any, nutritional supplements or formulas the child takes. Parents should also be asked how often and at what dosage the child takes of each supplement.

15.7 STEROID USE

As of October 2014, data on steroid use will no longer be collected.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 16: BLOOD PRESSURE MEASUREMENT

16.1 OVERVIEW OF BLOOD PRESSURE MEASUREMENT

This section describes the procedures that are to be performed to obtain correct measurement of blood pressure. Correct measurement of blood pressure is of the utmost importance to the success of this study since hypertension has been shown to be linked to the progression of CKD in children.

In the CKiD Study, blood pressure should be measured at every visit in a resting state using the Mabis Medic-Kit aneroid sphygmomanometer. Manual blood pressure measurement was chosen for CKiD because oscillometric devices may not be comparable between institutions and pediatric blood pressure normative values are based upon manual blood pressure measurements.

It is essential that the procedures described for measuring blood pressure be followed exactly. Precision is essential for valid blood pressure measurements since a specific aim of CKiD is to prospectively examine the influence of blood pressure and other cardiovascular risk factors on the progression of CKD in children.

16.2 BLOOD PRESSURE MEASUREMENT STEP BY STEP (Outline)

A. Equipment and Supplies:

- _____ (1) Mabis Medic-Kit Aneroid Sphygmomanometer
- _____ (2) Mabis Medic-Kit Cuffs - full set of 5 sizes
- _____ (3) Stethoscope with a bell (pediatric head preferred)
- _____ (4) Table at heart level to support arm
- _____ (5) Accusplit (model 80226) Stopwatch (provided in CKiD starter package)
- _____ (6) Measuring tape
- _____ (7) Black ball point pen
- _____ (8) Physical Exam Form (PE)

B. Arm Measurements

The following steps are properly carried out:

- _____ (1) Participant standing
- _____ (2) Arm bare from elbow to shoulder
- _____ (3) Arm at 90 degree angle
- _____ (4) Arm length measured from the acromion (or bony extremity of the shoulder girdle) to the olecranon (or tip of the elbow)
- _____ (5) Midpoint of arm marked at dorsal aspect
- _____ (6) Arm relaxed at side
- _____ (7) Measure arm circumference with tape horizontal
- _____ (8) No indentation of skin

- _____ (9) Mark at midpoint of arm
- _____ (10) Value checked with on the PE form to ascertain proper cuff size
- _____ (11) Proper cuff size checked on the PE form

C. Preparation for BP Readings

- _____ (1) Brachial artery palpated
- _____ (2) Midpoint of bladder within the cuff located
- _____ (3) Cuff applied with midpoint of bladder over brachial artery
- _____ (4) Arm positioned with midpoint of cuff width at "heart" level; lower edge 2 to 3 cm (1 inch) above crease
- _____ (5) Wait 5 minutes
- _____ (6) Mabis Medic-Kit Aneroid sphygmomanometer connected to cuff
- _____ (7) Sphygmomanometer scale is at eye level
- _____ (8) radial pulse located
- _____ (9) Cuff is inflated quickly to 60 mm Hg
- _____ (10) Cuff is further inflated slowly by increments of 10 mm Hg (if pulse present at 60 mm Hg) until the pulse is no longer felt.
- _____ (11) Cuff is quickly and completely deflated
- _____ (12) Observed Pulse Obliteration value is correctly recorded on the PE form
- _____ (13) The Correct Pulse Obliteration Pressure + 30 are added to get the Peak Inflation Level

D. Measurement of Blood Pressure

- _____ (1) Brachial artery palpated
- _____ (2) Stethoscope in ears
- _____ (3) Bell over artery, without cuff or tubing contact
- _____ (4) Cuff inflated quickly and smoothly to the Peak Inflation Level
- _____ (5) Deflation at 2 mm Hg/second to 10 mm Hg below K5
- _____ (6) Cuff quickly and completely deflated
- _____ (7) Cuff disconnected
- _____ (8) Recording of SBP and DBP values on the PE form

E. Between Readings

- _____ (1) Cuff removed or tubing disconnected if uncomfortable
- _____ (2) Arm raised passively overhead for 15 seconds. (Make sure the patient is not supporting the arm at all)

- _____ (3) Arm lowered and cuff replaced with attention to brachial artery and midpoint of bladder; lower edge 2 to 3 cm (1 inch) above crease of the elbow. Note: There is a total of 30 seconds between readings.
 - _____ (4) Cuff reconnected
- F. Second Seated Blood Pressure Reading
- _____ (1) Conforms with procedures as in E above
- G. Third Seated Blood Pressure Reading
- _____ (1) Conforms with procedures as in E above
- H. Completion
- _____ (1) Complete PE Form
 - _____ (2) Closure of Mabis Medic-Kit Aneroid manometer case for storage

16.2 BLOOD PRESSURE MEASUREMENT STEP BY STEP (Detailed)

16.2.1 Overview

In this section, the step-by-step procedures for blood pressure measurement in the CKiD study are presented. It should be emphasized that the steps outlined here can satisfactorily be followed for the vast majority of child subjects participating in ambulatory follow-up. Exceptional situations do arise, with sometime serious obstacles to successful blood pressure measurement. The training program for a particular setting must include guidelines for handling such exceptions. Only a few will be noted. It will be the responsibility of the Clinical Coordinating Centers (to be named) and in the Data Coordinating Center (Jeanne Charleston) to encourage observers to note exceptional circumstances and to seek consultation with the DCC (Jeanne Charleston) when they arise so that participants will be appropriately evaluated. Mabis Medic-Kit sphygmomanometers should be used for blood pressure measurement for all CKiD clinic visits and for the determination of peak inflation levels. This section of the Manual of Procedures will concentrate on this device.

It should be noted also that the procedures listed here are illustrated in the third lecture presentation, "Blood Pressure Recording Procedures" (Section 27.2.3.3).

16.2.2 Preparation for Blood Pressure Measurement

Some of the many extraneous factors influencing blood pressure are controlled by standardizing the measurement technique and the environment in which the measurement is made. Uncontrolled factors (time of day, identity of the observer) are recorded, so that they can be taken into account during analysis.

Participants and/or parents should be instructed that the child is to abstain from caffeine, smoking, and exercise at least one-half hour prior to and until completion of the blood pressure measurement as appropriate. Current drug intake, including medications affecting blood pressure and non-prescription drugs, should be recorded on the day of the examination on the Medication and Supplement Inventory Form.

Try to keep the environment where blood pressure measurements are performed as pleasant as possible. Children and their parents should be given a full explanation and instructions about the preparation for the blood pressure examination and an opportunity for brief questions. The setting in which blood pressure measurements are made should take place in a separate, quiet room where no other activity is taking place, and where temperature fluctuations are minimal. Equipment (including PE form, sphygmomanometer, etc.) should be checked and waiting for the participant.

Allow five minutes of rest in this quiet room after arm measurement but before pulse is measured which occurs prior to taking the blood pressure. Explain to the child that the five-minute rest period will provide for more valid blood pressure measurements. Preferably, at this time, the observer should leave the room. The child should be seated with back supported with legs uncrossed and feet comfortably flat on the floor, not dangling. The patient should also be instructed to refrain from playing with video games, using a cell phone, or other activities that may affect blood pressure.

Blood pressure should not be taken with the child sitting on an examining table. The BP measurement is best taken by having the child seated in a chair next to a work table, having their right arm supported by the table, so that the BP cuff is at the level of the heart. If a measurement cannot be made on the right arm (due to casting, or fistula placement, etc.) then the BP should be taken on the left arm.

16.2.3 Blood Pressure Measurement Procedures

All blood pressure measurements taken by CKiD personnel should be obtained using the Mabis Medic-Kit Aneroid sphygmomanometer.

The sitting arm blood pressure is measured three times at each clinic visit. It takes approximately 15 minutes to obtain three blood pressure measurements including the initial five-minute rest.

Blood pressure equipment should be checked prior to seeing the participants. Once a participant is given instructions and explanations blood pressure measurement begins. The following steps must be followed precisely.

All blood pressure measurements conducted by CKiD Study Personnel on CKiD patients must be recorded on the PE forms, regardless of the clinical condition of the patient at the time of the measurement. If more than one blood pressure measurement is obtained on the same patient on the same day, then:

1. The Physical Exam Form (PE Form) must be completed for each blood pressure measurement that is taken.
2. The Physical Exam Form must be mailed with the other forms to the Clinical Coordinating Centers for data entry.
3. The complete CKiD protocol for blood pressure measurements must be followed for each measurement

Blood pressure measurements conducted by CKiD personnel on CKiD participants should be conducted at the CKiD clinical sites.

16.2.4 Stethoscope

A standard Littman stethoscope (or other comparable stethoscope) with a bell is used. A stethoscope with a pediatric head is recommended as the bell is small enough to be used on the arms of infants and small children. Korotkoff sounds are best heard with the bell because of their low pitch. Stethoscope tubing should be about 12 to 15 inches from the bell piece to "Y" branching. This length provides optimal acoustical properties and allows the observer to read the sphygmomanometer at eye level and in a comfortable position. Earpieces should fit comfortably and snugly in the ears. Four points should be observed in using the stethoscope.

1. The earpieces should be directed forward into the external ear canal.
2. The earpieces should be tight enough to exclude outside sound but not so tight that they cause discomfort.
3. The valve between the bell and the diaphragm should be turned in the direction of the bell.
4. The bell of the stethoscope should be placed lightly on the skin overlying the brachial artery - immediately below, but not touching, the cuff. The brachial artery is usually found above the crease of the arm, slightly towards the body. Light pressure accentuates low-pitched sound and avoids compression murmurs. Pressing too heavily with the stethoscope over the brachial artery causes turbulent flow in the artery and a murmur can be heard which may prolong the apparent duration of fourth-phase Korotkoff sounds.

16.2.5 Arm Measurement and Cuff Sizes

The proper cuff size must be used to avoid under- or over-estimating the correct blood pressure. Recently issued pediatric guidelines on cuff size have simplified the cuff selection process by stating that proper blood pressure measurement will be achieved so long as the length of the cuff bladder is equal to 80-100% of the arm circumference. To determine the proper cuff size, the observer must measure the arm circumference at the midpoint of the arm at each visit. This procedure follows:

1. Expose (bare) the right arm from the shoulder.
2. With the participant standing, holding the forearm horizontal, measure the arm length from the acromion (or bony extremity of the shoulder girdle) to the olecranon (or tip of the elbow) with a plastic coated metric tape.
3. Mark the midpoint on the dorsal surface with a pen.
4. Instruct the participant to relax the arm along the side of the body.
5. Measure the arm circumference by drawing the tape snugly around the arm at the level of the midpoint marking. Care must be taken to keep the tape horizontal and the tape should not indent the skin.
6. Record on the PE form the arm circumference measurements and corresponding cuff sizes (shown below).
7. Check the indicated cuff size on the PE form.

Since arm circumference may change over the course of the study due to growth, this measurement procedure should be repeated at each visit where blood pressure is to be measured. **Do not use the cuff itself as a measurement device because the ranges marked on the cuff may not correspond with the table.**

Determination of Cuff Size Based on Arm Circumference

<u>Arm Circumference</u>	<u>Cuff Size (Mabis Medic-Kit)</u>
9 to 14.0 cm	Infant
>14.0 to 21.0 cm	Child
>21.0 to 29.0 cm	Adult, Regular
>29.0 to 40.0 cm	Large Adult
>40.0 to 52.0 cm	Thigh

16.2.6 Application of the Blood Pressure Cuff

The appropriate cuff (as determined in the arm measurement procedure) is placed around the upper right arm so that the midpoint of the length of the bladder lies over the brachial artery and the mid-height of the cuff is at heart level. The lower edge of the cuff, with its tubing connections, should be placed about 1 inch above the natural crease across the inner aspect of the elbow. The cuff is wrapped snugly about the arm, with the palm of the participant's hand turned upward. The wrapped cuff should be secured firmly by means of the Velcro on the cuff.

16.2.7 Determining the Peak Inflation Level

For each participant it is necessary to determine the pressure level to which the cuff is to be inflated for accurate measurement of the systolic pressure. This is because the pressure at the start of the reading should always exceed the systolic blood pressure, otherwise the first of the Korotkoff sounds will be missed (see Lecture #1). This starting pressure is called the Peak Inflation Pressure and is determined as follows.

- First, the cuff tubing should be attached to the Mabis Medic-Kit Aneroid sphygmomanometer.
- While palpating the radial pulse (at the wrist), observe sphygmomanometer and inflate the cuff rapidly to 60 mmHg and then slowly inflate in increments of 10 mmHg until the pulse is no longer felt.
- If the pulse is still felt, the cuff pressure should be increased until the pulse disappears. Either the first or the second of these procedures will identify the Observed Pulse Obliteration Pressure. Record on the PE Form.
- When this has been detected, the cuff is quickly and completely deflated.
- The Observed Pulse Obliteration Pressure is then added to 30 mmHg.
- This summed value is the Peak Inflation Level. The cuff is to be inflated to this level for all readings at this examination.

NOTE: All readings on the sphygmomanometer are made to the nearest even digit. Any reading that appears to fall exactly between markings on the column should be read to the next marking immediately above, i.e., 2, 4, 6, 8, or 0.

16.2.9 Blood Pressure Readings

Next, the observer should proceed to carry out the first blood pressure reading. Detailed instructions are given below for measuring blood pressure with a Mabis Medic-Kit Aneroid sphygmomanometer.

16.2.10 Measuring Blood Pressure with a Mabis Medic-Kit Aneroid Device

The steps for readings with the Mabis Medic-Kit Aneroid device are described below.

- (1) Wait at least 30 seconds after complete deflation of the cuff following any preceding inflation. Palpate the brachial artery at the elbow, slightly toward the elbow. Mark with a pen the location of the palpated artery.
- (2) Connect the cuff to the Mabis Medic-Kit Aneroid device.
- (3) Place the ear pieces of the stethoscope into the ears, with the tips turned forward.
- (4) Apply the bell of the stethoscope over the marked brachial artery location, just below but not touching the cuff or tubing.
- (5) Using the previously determined peak inflation level, rapidly inflate to this level. The eyes of the observer should be focused on the dial of the aneroid sphygmomanometer. The observer should rapidly inflate the cuff.
- (6) By slightly adjusting the valve, deflate and maintain a constant rate of deflation at approximately 2 mm Hg per second, allow the cuff to deflate, listening throughout the entire range of deflation, from the maximum pressure past the systolic reading (the pressure where the first of two consecutive beats is heard), until 10 mm Hg below the level of the diastolic reading (that is, 10 mm Hg below the level where the last of two consecutive beats is heard).
- (7) Open the valve to deflate fully and disconnect the tubing. Remove the stethoscope earpieces from the ears.

- (8) Record the systolic and diastolic reading on the PE form.
- (9) Repeat steps 3 through 9 two more times, waiting at least 30 seconds after complete deflation of the cuff following any preceding inflation. These are the Second and Third Mabis Medic-Kit Aneroid Blood Pressure Values. Note: After the first and second readings, the patient's arm should be raised for 15 seconds. The arm is then lowered. Wait an additional 15 seconds. There is a total of 30 seconds between readings.
- (10) Ways to accentuate Korotkoff sounds: 1) While using the standard technique, rapidly inflate the cuff while the participant's arm is elevated, then, bring the participant's arm back to heart level and begin taking the reading. Or, 2) After the cuff is rapidly inflated to the Peak Inflation Level, have the participant rapidly open and close his or her fist six to eight times. Then, instruct the participant to relax their arm and begin taking the reading.

16.2.11 Criteria for Systolic and Diastolic Blood Pressure

To correctly identify the 1st-phase (systolic) and 5th-phase (diastolic) Korotkoff values, the observer must listen carefully via the stethoscope while reading and interpreting the aneroid dial. The systolic value can be identified as the pressure level where the first of 2 or more consecutive beats are heard in appropriate rhythm. The diastolic value can be identified as the pressure level where the last of two consecutive beats heard. The aneroid dial should be made to drop at 2 mm Hg per second, from the maximum pressure until 10 mm Hg below that of the last regular sound heard. The control of the deflation rate is essential for accurate readings and depends on handling of the bulb and its control valve.

PLEASE NOTE: A single sound heard in isolation (i.e., not in rhythmic sequence) before the first of the rhythmic sounds (systolic) or following the last of the rhythmic sounds (diastolic) does not alter the interpretation of the blood pressure.

In some patients, the disappearance of sound, i.e. the fifth Korotkoff sound, never occurs and beats can be heard during the entire deflation period. In these circumstances, the fourth Korotkoff sound should be used to determine the diastolic blood pressure. The fourth Korotkoff sound at the point during deflation where the quality of the sound changes dramatically (e.g. the quality of the beat becomes muffled).

16.2.12 Forgotten Blood Pressure Readings

If for any reason the observer is unable or has forgotten to complete any portion of the PE exam, and the participant is gone, leave the items blank on the paper form. If a blood pressure value is missed or forgotten, completely deflate the cuff and start over with a replacement reading after the proper interval. Do not re-inflate the blood pressure cuff during a reading. However, under no other circumstances may a replacement reading be obtained. Once the study measurement procedure has begun, record all observations. Do not redo a reading that looks unusual to you.

16.2.13 Reporting the Blood Pressure Results to the Participant

The patient may wish to know his or her results before the form is sent to the Clinical Coordinating Center for data entry. If so, average the first, second, and third Mabis Medic-Kit Aneroid readings and give the results to the participant. State clearly the systolic and diastolic pressures and offer to write down these values for the participant.

16.3 ACKNOWLEDGMENT OF ADAPTION

AASK Cohort
Blood Pressure Measurement
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Adapted By
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by Darwin R. Labarthe and Melanie Palmer

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Based on the Procedures
of the Hypertension Detection and Follow-up Program (HDFP)

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Gary R. Cutter, Ph.D.
Barbara H. Casey, B.A.

Some text adapted from the ARIC Protocol 11:
"Sitting Blood Pressure and Postural Changes" (4/16/87)

16.4 REFERENCES

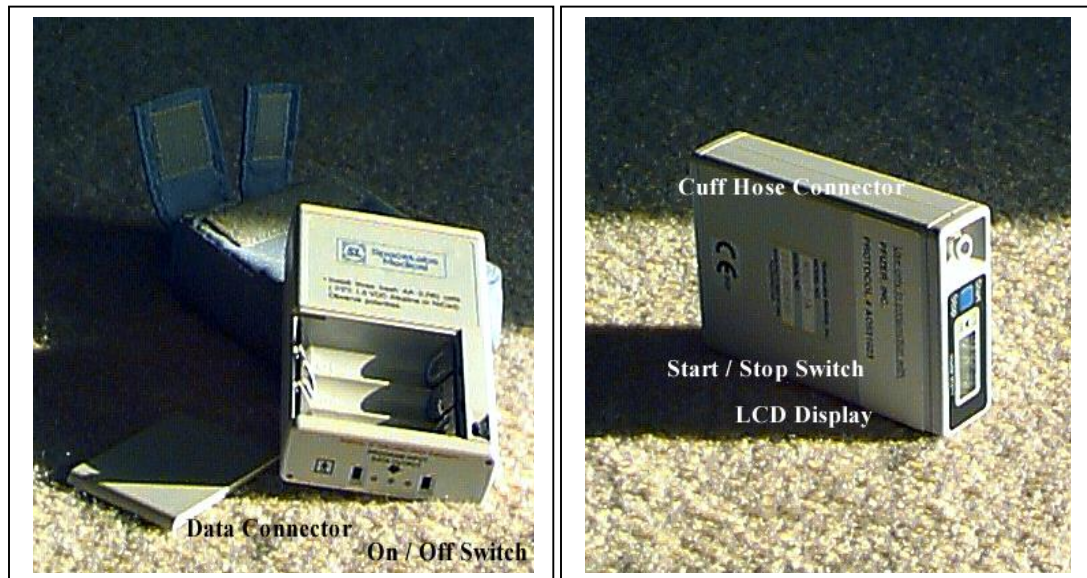
1. Writing Committee on behalf of the HDFP Cooperative Group: The Hypertension Detection and Follow-up Program. Prev Med 5:207-315, 1976.
2. The Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group: Rationale and Design of a Randomized Clinical Trial on Prevention of Stroke in Isolated Systolic Hypertension. J Clin Epidemiol 41:1197-1208, 1988.
3. Perloff D, Grim C, Flack J, Frohlich ED, Hill M, McDonald M, Morgenstern BZ: Human Blood Pressure Determination by Sphygmomanometry. Circulation 88:5, 1993.
4. Prineas RJ: Blood Pressure Sounds: Their Measurement and Meaning. A Training Manual. Gamma Medical Products Corp., Philadelphia, 1978.
5. Wright BM, Dore CF: A Tyco Classic Aneroid Sphygmomanometer. Lancet 1:337-338, 1970.
6. Labarthe DR, Hawkins CM, Remington RD: Evaluation Performance of Selected Devices for Measuring Blood Pressure. Am J Cardiol 32:546-553, 1973.
7. Evans JE, and Rose G. Hypertension. Brit Med Bull 27:37-42, 1971.
8. Rose GA. Standardization of Observers in Blood Pressure Measurement. Lancet 1

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 17: AMBULATORY BLOOD PRESSURE MONITORING

17.1 THE SPACELAB 90217 AMBULATORY BLOOD PRESSURE MONITOR

This section describes the procedures that are to be performed to obtain Ambulatory Blood Pressure using the SpaceLabs 90217 Ambulatory Blood Pressure monitor. This monitor is an extremely reliable device for the frequent collection of blood pressure data while the participant is ambulatory. It uses the oscillometric method of measuring blood pressure. The size, weight and efficiency with which a BP measurement is performed position this monitor as a comfortable and acceptable device for patient care.



In the above picture the monitor features are identified.

- **4 digit LCD** displays the results of a blood pressure reading, error codes to help diagnose problems, communication codes confirming monitor data connections, and the time when readings are not being performed.
- **Batteries** - uses three (3) AA size batteries, rechargeable or alkaline. These batteries can be removed without any change to the data contained in the monitor. They are used only for pressurizing the arm cuff.
- **Communications port** for connecting the monitor to a computer or modem.
- **Blue Start / Stop switch** - used for manually starting a BP reading
- **Black On / Off switch** - used to power on or power off the monitor.
- **Cuff hose connector** - the tube to the arm cuff attaches here using finger tight pressure. No tools are needed.
- Lithium battery (not pictured) is internal to the monitor and ensures that initialization configuration and monitoring data are retained until a computer download is performed.

Three Important Points

- The monitor sent to you from the ABPM Coordinating Center will already be initialized. **Make sure you do not re-initialize the monitor.**
- Do not change batteries without contacting the ABPM Coordinating Center.
- Previously collected monitoring data is **NOT** impacted by changing or removing the monitor AA batteries. It is also **NOT** impacted by turning the monitor on or off. Do **NOT** mix rechargeable batteries with non-rechargeable batteries.

17.2 REQUESTING A MONITOR FOR AN ABPM PROCEDURE

Monitors will be provided by the ABPM Coordinating Center. In order to obtain a monitor, certain critical information must be provided to the ABPM Coordinating Center via the “ABPM Monitor Request” form in Coordinator’s Corner on the CKiD website (17.2.1 for details). Upon receipt of the monitor request, an ABPM will be reserved for that participant. The study coordinator will perform the participant education, monitor placement, participant demographics collection, and ensure monitor return from the participant. Upon receiving the monitor back from the participant, the study coordinator should return the monitor to the ABPM coordinating center for download and analysis. In rare cases where it is more convenient for participants to return the monitors directly to the ABPM coordinating center, a self-addressed FedEx shipping label should be provided to the participants with instruction on returning the monitor (see Section 17.6 for details.) The site should follow up with the participant to ensure the monitor is returned promptly.

17.2.1 Steps to Submit Monitor Request

1. Go to Coordinator’s Corner on the CKiD website <https://statepi.jhsph.edu/ckid/admin/coordinator.html> and click on the ABPM Monitor Request link. For your site’s username and password, contact Judith Jerry-Fluker at jjerry@jhu.edu. The form must be completed prior to the study visit date to allow sufficient time for the monitor to be shipped out and received at your site.
2. Fill out the following fields on the ABPM Monitor Request form:
 - Requester’s Email Address
 - Site #
 - Site Name
 - Scheduled Visit Date
 - CKiD ID#
 - Visit #
 - Site Contact Information:
 - i. Name of person to contact if there are any questions
 - ii. Address, room # (if applicable), city, state, and zip code of location that the monitor will be shipped to
 - iii. Phone number of contact person
 - iv. Comments, if applicable
3. Click on the submit button and the ABPM Center will receive an email containing your request.
4. The ABPM Center will send an email verifying the request information if necessary and a monitor will be reserved for the participant’s visit.

5. Your monitor will be sent via FedEx to you using business 3 day delivery in most cases. If the monitor is needed urgently, it can be overnighted to you but this is expensive and consumes the study budget. The shipment will contain the following:
 - ABPM monitor/cuff
 - ABPM Diary (see Section 17.4.1)
 - ABPM Letter (see Section 17.4.2)
 - Return instructions (see Section 17.6)
 - Coordinator Cheat Sheet (modified version of Section 17.3)An ABPM Participant Instructions brochure will be included in the study visit binder for these visits. In addition, section 17.5.3 includes an ABPM Troubleshooting Sheet that lists common error codes and recommended solutions.
6. The ABPM coordinating center will contact you if any information is missing or if the monitoring was unsuccessful and should be attempted again.

After the ABPM center receives the request, the ABPM center will obtain the participant's most recent mid-arm circumference measurement from the Nephron Data Management website's Visit Control Sheet Report. If the coordinator is aware that the participant has had significant growth/change since the previous mid-arm circumference was documented, two cuff sizes may be requested via the comments section of the ABPM Monitor request form. Otherwise, the ABPM Center does the following to obtain the participant's most recent mid-arm circumference measurement from the Visit Control Sheet:

- Go to <https://statepiaps.jhsph.edu/nephron/groups/aspproc/>
- Type in username and password (For your site's username and password, contact Judith Jerry-Fluker at jjerry@jhu.edu.)
- Click on Report Menu
- Select Visit Control Sheet and press submit
- Enter KID and press submit
- Click Submit for the Visit # of the upcoming visit (i.e., if site is requesting a monitor for V6 visit, then click the submit button to the right of V6)
- Identify the participant's most recent mid-arm circumference measurement taken at the last CKiD visit.

After the ABPM Center obtains the mid-arm circumference measurement, the monitor will be shipped to the coordinator.

17.3 PLACING THE MONITOR ON THE PARTICIPANT

Placing the monitor on the participant is a critical part of the BP measuring process for two main reasons. The **first** reason is to set a good example for the participant to follow during their monitoring because compliant participant behavior is critical to an effective monitoring. It is also important to familiarize the participant with the various components of their monitoring: the monitor controls, the cuff, the hose, and the diary. The participant will need to remove the monitor anytime there is danger of the monitor getting wet so it is important to involve the participant in the process of placing the monitor. The **second** reason is to obtain 3 blood pressure readings using the ABPM device to ensure it is working properly.

Remember to fill out the top left section of the diary before sending the ABPM home with the participant.

The Mabis Medic BPs should be recorded on the participant diary.

(Mabis Medic BPs are recorded on page 5 of the Physical exam form)

The BP readings obtained during the visit using the ABPM device are to test the monitor and should not be recorded on the diary.

17.3.1 Placing the Cuff

1. The ABPM Center will send the proper cuff based on the arm measurement taken at the previous visit. On day of visit, confirm mid-arm circumference measurement and compare it to the cuff size received from the ABPM Center. For assistance, refer to the Guidelines for Cuff Selection chart (see Section 17.5.) In some instances, two cuffs will be sent if the participant's mid arm circumference falls between two cuff sizes, or if the study coordinator requests two cuff sizes via the comments section of the ABPM Monitor request form. Always choose the largest cuff size that can be used as an undersized cuff typically produces an elevated blood pressure reading.
2. Be sure the cuff size, arm circumference, age, height, weight, and 3 **Mabis Medic blood pressures** (also referred to as casual or manual BPs) are recorded on the top left section of the participant diary. Do not document the "Dinamap" blood pressure.
3. Place the cuff on the non-dominant arm with the artery arrow pointed down at the interior of the elbow. The illustration below is a good example of proper cuff placement. **Make sure the participant and parent are aware and demonstrate how to place cuff. The cuff should be tight enough so it doesn't fall down but loose enough that one finger fits under cuff.**



Note: Ensure that the cuff velcro has **at least 3 inches of overlap** and the pressure hose is exiting at the top of the cuff.

4. Place hose up through the participant's shirt then down toward his/her waist where you can attach to the monitor.
5. Connect the pressure hose to the fitting on the monitor by pushing the hose until you hear the metal connector click. Verify that the hose is connected correctly by gently tugging on the metal connector.

6. Either fasten with a belt or place the monitor in a pocket. The illustration below is a good example of proper monitor placement.



7. Turn the monitor on. (This is the black switch on the side of the monitor.)
8. **Press the Blue Start / Stop button to begin the first ABPM practice reading.** Help the participant note how the monitor counts down and then pressurizes the cuff. Note the cuff pressure in the LCD window and **explain to the participant that this will be visible only until the fourth reading has been taken.**
9. **It is important to test the ABPM with 3 practice readings before the participant leaves.** These ABPM BP readings should not be documented. Instead the clinical Mabis Medic BPs must be recorded in the top left section of the participant diary.
10. Upon completion of the first ABPM practice reading, take a moment to review the importance of diary recordings. Emphasize the importance of documenting the time the participant goes to **sleep**, the time they **wake** up (even if they are lounging in bed for a while after waking up), and the time(s) of any **medication** administration (all antihypertensive medications and dosage should be specifically noted). Refer to the diary example in Section 17.4 for examples.
11. Upon completion of the diary explanation, **press the Blue Start / Stop button again and take the second ABPM practice reading.** Take this opportunity to illustrate for the participant how to limit activity while the ABPM is measuring BP every 20 minutes. The participant should relax their arm at their side until the cuff fully inflates and then deflates. The monitor will not take the reading if the arm is bent, tense, twitching, above the heart, or holding a heavy object but will result in an error readings indicated by a rapid 3 beep warning. In the event of an error, the device will try to measure BP once again after 3 minutes of rest. **Remember: the BPs obtained using the ABPM device should not be recorded on the diary.**
12. Explain that the monitor takes a blood pressure reading every 20 minutes for a total of 24 hours and **they will not see the reading!** Repeat this explanation several times during the participant instructions.
13. Address any questions the participant might have, review the instructions one more time, then **press the Blue Start / Stop button and take the third ABPM practice reading.** Three ABPM practice readings must be done before allowing the participant to leave with the monitor and begin their ambulatory measurement.
14. Remind the participant that the monitor is not waterproof and cannot get wet. The monitor must be removed for bathing, showering, swimming, etc. as well as for contact sports such as football and basketball. The monitor must be turned off using the black button on the side, and the cuff taken off while showering or engaged in other water activities. After the water activity is finished, put cuff on and turn on monitor using black button. The three ABPM practice readings do not need to be repeated. They should not forget to turn the monitor back on!!!
15. Ensure the participant has the diary, site contact numbers, and understands the instructions. This entire process should have taken between 15 and 20 minutes.
16. Instruct the participant to turn off the monitor, using the black switch, after 24 hours.

17. If the 24 hour monitoring is not started (i.e., monitor is not worn) at the clinic site, the site should remind the family to place the device on the participant within **one week** of the study visit. If the 24 hour monitoring is started at home, the three ABPM practice readings should still be collected at the study visit to ensure the device is working before the participant leaves. The participant does not need to repeat these practice readings when starting the monitor at home.
18. In the rare cases in which the ABPM device is started **more than one month** after the study visit, then the participant's Mabis Medic auscultatory blood pressures must be obtained again when the ABPM device is placed on the participant (i.e., the participant should return to the clinic so that the Mabis BP measurements can be repeated and documented on the ABPM diary.) If the family is unable to return to the clinic or the site is unable to schedule a time to place the ABPM device on the participant, then the site should contact their respective CCC for further instructions.
19. Remind the participant the following key points:
- It's important that the ABPM be worn for a full 24 hour consecutive period.
 - If the monitor is removed for more than one hour, add the time that it was removed to the end of the 24 hrs. (i.e., If the monitor was removed for 2 hours, the monitor would be worn for 26 hours rather than 24 hours).
 - Blood pressure readings while sleeping may be the most important. Please make every effort to keep the monitor on when you're asleep so it can continue recording your blood pressure. If too many hours are missed, we will not be able to analyze any of the data.
 - The monitor will take a reading every 20 minutes. During the day it will beep to alert you when it is about to take a reading. (Note: There will not be a beep during night hours, between 8pm-8am).
 - When the cuff inflates, the participant's arm should be relaxed and still. If possible, stop your activity and remain motionless during the reading.
 - After blood pressure is taken, a single soft beep indicates that the BP was taken correctly. If there are several quick beeps, then an error has occurred and the machine will try again in 3 minutes.
 - Check to be sure that:
 - The cuff is not too loose or too tight
 - The artery arrow on the cuff is pointed down at the interior of the elbow
 - The hose is not kinked or disconnected
 - The hose is connected tightly to the monitor
 - At night, place the monitor box to the side of the bed or, if the noise of the monitor is bothersome, place the monitor under a pillow to muffle the noise.
 - On the diary page, remember to record:
 - The time you go to sleep
 - The time you wake up
 - Medications you take (and what time you take them)
 - Any type of exercise you do
 - At the end of the recording time, the monitor should be turned off with the black ON/OFF switch and returned as quickly as possible.

17.4 PARTICIPANT DIARY AND ABPM LETTER

17.4.1 Participant Diary

Below is an **example** of the participant diary we utilize with our participants. This diary has worked well because it is a single page format that allows for the meticulous entry of daily events as well as the more general entry most participants practice. The top left section of the participant diary must be filled out by the clinical site study coordinator. **Make sure parents check diary for TIME AWAKE and TIME ASLEEP!**

The 3 Mabis Medic BPs should be recorded on the participant diary where indicated below. Do not document the ABPM or Dinamap BP readings here.

Ambulatory Blood Pressure Monitoring Diary

COORDINATOR TO COMPLETE THIS SECTION				Participant To Complete This Section		
CKiD ID:	<input type="text"/>			Date worn:	<input type="text"/> month / <input type="text"/> day / <input type="text"/> year	
Monitor SN:	<input type="text"/>			Time went to sleep:	: <input type="text"/> AM/PM <small>Circle</small>	
Visit Date:	<input type="text"/>			Time woke up:	: <input type="text"/> AM/PM <small>Circle</small>	
Return Date:	<input type="text"/>			*SLEEP TIME* *WAKE TIME* are very important for the analysis of your blood pressure		
Cuff size:	<input type="text"/>			Participant Activity and Medications Diary:		
Arm (cm):	<input type="text"/> cm	Ht (cm):	<input type="text"/>	Time	Description	Meds Taken
Age (years):	<input type="text"/> years	Wt (kg):	<input type="text"/>	10:20 <small>Circle</small> AM/PM	Took Meds (example)	1,3,4
Mabis Medic Blood Pressures:				: AM/PM		
	#1	#2	#3	: AM/PM		
Systolic:	<input type="text"/>	<input type="text"/>	<input type="text"/> mmHg	: AM/PM		
Diastolic:	<input type="text"/>	<input type="text"/>	<input type="text"/> mmHg	: AM/PM		
Participant To Complete This Section						
Medication Name	Dose	Schedule				
Ex: Lisinopril	5 mg	2 x day	<input type="checkbox"/> No medications taken			
#1:	<input type="text"/>	<input type="text"/>				
#2:	<input type="text"/>	<input type="text"/>				
#3:	<input type="text"/>	<input type="text"/>				
#4:	<input type="text"/>	<input type="text"/>				
#5:	<input type="text"/>	<input type="text"/>				
#6:	<input type="text"/>	<input type="text"/>				
#7:	<input type="text"/>	<input type="text"/>				
#8:	<input type="text"/>	<input type="text"/>				
#9:	<input type="text"/>	<input type="text"/>				
				: AM/PM		
				: AM/PM		
				: AM/PM		
				: AM/PM		
				: AM/PM		
				: AM/PM		
				: AM/PM		
				: AM/PM		

A copy of the ABPM diary will be shipped with each monitor. This diary can also be downloaded from the CKiD website. Request for an electronic diary should be sent to ABPM@uth.tmc.edu.

17.4.2 ABPM Letter

During the academic school-year, participants will be asked to wear the monitor to school. Study Coordinators should provide the family with a letter for the participant to take to school. If the participant has gym class or some other physical activity, the letter should be provided so the participant can be excused from participation. Below is an example of the family ABPM letter that will be included with each monitor shipped. Write in the date, participant's date of birth and participant's name. This letter can be sent by email if requested.



Date:

RE: ABPM Monitor

DOB: _____

To Whom It May Concern:

_____ is currently wearing a special blood pressure monitor. This will remain in place for 24 hours and functions completely automatically. She/he may participate in her/his usual activities while wearing the monitor except for gym class or sports practice. Please excuse her/him from gym or practice if applicable.

Please feel free to contact us if you have any questions about this matter.

Sincerely yours,

Division of Pediatric Nephrology

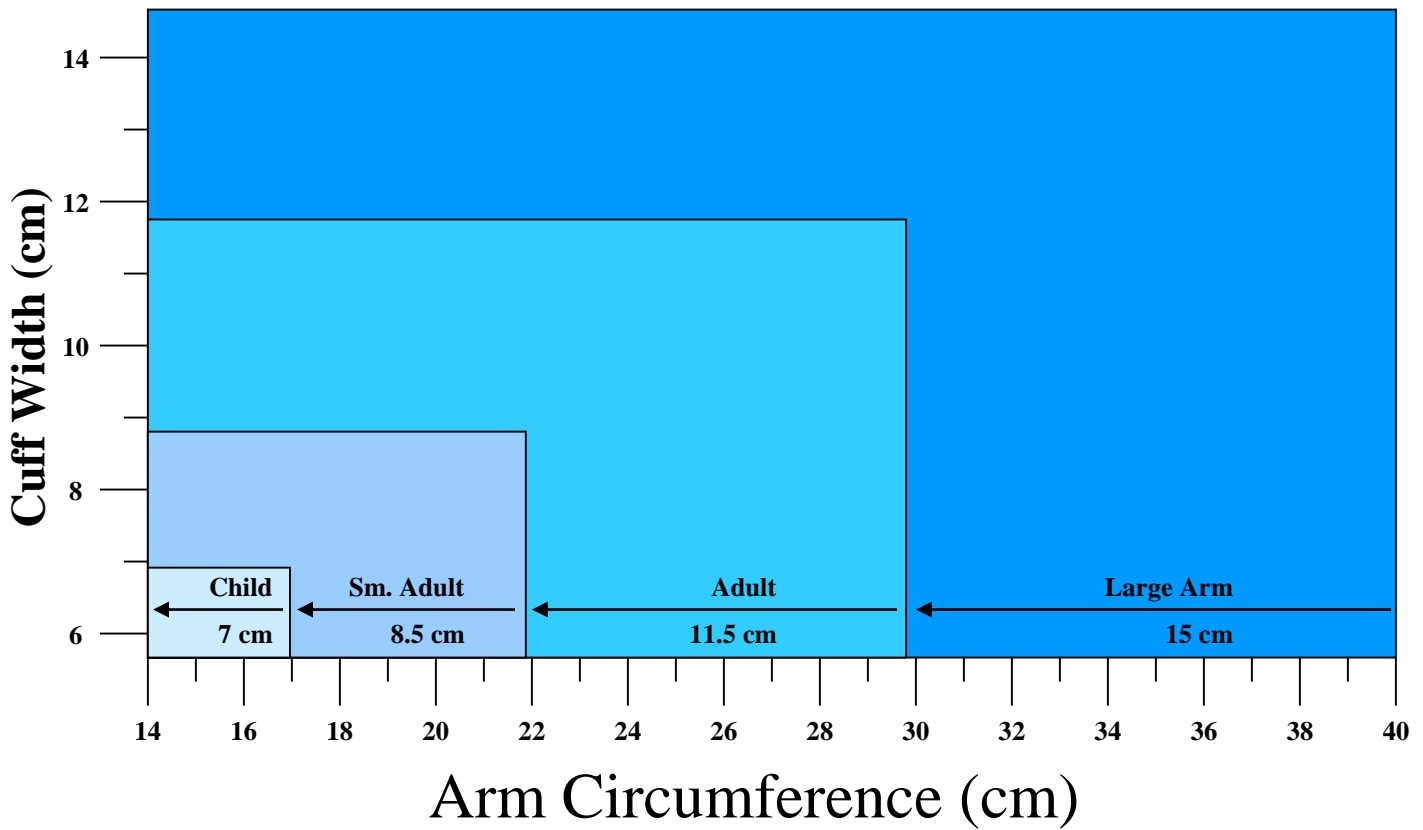
17.5 SPACELAB GUIDELINES

17.5.1 Guidelines for Cuff Selection Using SpaceLabs ABPM Cuffs

Below is a chart generated by Dr. Craig Belsha etc.

Guidelines for Cuff Selection SpaceLabs ABPM Cuffs

$$\frac{\text{Cuff Width}}{\text{Arm Circumference}} = 0.4 - 0.5$$



Courtesy of Dr. Craig Belsha

17.5.2 SpaceLabs Event Codes for Model 90217A (adapted from SpaceLabs ABPM Operations Manual 070-2039-00 Rev. C)

The monitors display an event code whenever an event prevents the monitor from successfully completing a blood pressure measurement. The two numerical digits of the event code indicate the reason the measurement was aborted. The table below lists events codes that are displayed on the monitor, as well as event codes that appear on the Event Code Report.



Monitor	Report	Condition
EC00		
	EC10	Excess movement artifact. Frequent EC10 messages may indicate an air leak.
	EC20	A) A very large number of movement artifacts B) Heart rate arrhythmia
	EC30	A) Movement artifact at mean arterial pressure B) Heart rate arrhythmia
	EC40	A) Movement artifact at systole B) Heart rate arrhythmia
	EC50	A) Movement artifact at diastole B) Heart rate arrhythmia
	EC60	A) Movement artifact B) Heart rate arrhythmia
	EC70	Systole was found to be above the highest cuff pressure. However, this result appears to be an error caused by motion artifact. Therefore, the cuff will not be inflated to a higher pressure on the next measurement attempt.
	EC80	A) Movement artifact B) Heart rate arrhythmia
	EC90	A) Movement artifact B) Heart rate arrhythmia
EC01		
	EC11	Did not pump above the mean arterial level.
	EC21	Did not pump above systolic pressure.
	EC91	Systole appears higher than the selected maximum cuff pressure limit.
EC02		
	EC12	Did not reach initial cuff pressure. The cuff may have been improperly applied or there may be an air leak.
	EC22	Overpressure.
	EC32	Overpressure.
	EC42	No cuff attached.
	EC52	Kinked hose.
	EC62	Cuff applied too loosely.
	EC82	
EC03		
	EC03	Patient canceled reading by pressing STOP key. No retry attempt is made following an EC03 code.
	EC13	The Office Check mode has been reinstated. No retry attempt is made following an EC13 code.

Monitor	Report	Condition
EC04		
	EC04	Blood pressure measurement not completed in the maximum time allowed. Occasional EC04 messages may result from excessive patient movement. Frequent EC04 messages would indicate an improperly applied cuff or a monitor malfunction which requires service.
	ECn4	(where n = 1 to 9) Indicates that one or more of the blood pressure results have been corrupted and subsequently recovered. Frequent occurrence of this message would indicate a malfunction that requires service.
	EC05	The individual blood pressure result has been corrupted and cannot be recovered.
EC15		Equipment malfunction. Return to Spacelabs Healthcare for service.
EC25		Monitor failed to initialize. Please initialize.
EC35		90207 At least one of the blood pressures or time readings obtained before the event code is erroneous. Interpret all readings with caution. 90217/90217A The monitor needs to be reinitialized.
EC05		
EC05 & EC45	EC45	Invalid bleed size. The monitor has automatically changed the bleed size to 8mmHg.
EC05 & EC55	EC55	An unexpected loss of power possibly caused by: a) removal of the batteries during a blood pressure measurement, b) hardware overpressure, or c) a hardware time-out. Frequent EC55 messages would indicate a malfunction which requires service.
EC05 & EC65	EC65	90207 Equipment malfunction. Return to Spacelabs Healthcare for service. 90217/90217A Extremely large artifact.
EC05 & EC75	EC75	Equipment malfunction. Return to Spacelabs Healthcare for service.
EC05 & EC85	EC85	Equipment malfunction. Return to Spacelabs Healthcare for service.
EC05 & EC95	EC95	Cuff pressure baseline is out of limits. The monitor should correct the baseline automatically within 10 minutes, or it can be reset by initializing the monitor. If initialization does not correct the condition, the monitor must be returned to Spacelabs Healthcare for calibration.
EC07		
	EC78	Clogged connector filter.
EC08		
	EC18	Too few data entries to accurately determine blood pressure. This message may indicate that the cuff is not being worn by the patient (taken off but left connected to the monitor). The message may also indicate that motion artifacts cause the majority of the incomplete data.
	EC28	Diastole above 200mmHg.
	EC38	Pulse pressure less than 16mmHg.
	EC48	A) Movement artifact at mean arterial pressure B) Heart rate arrhythmia

17.5.3 ABPM Trouble Shooting Sheet

As with any machine, sometimes an error occurs that prevents the ambulatory blood pressure monitor from completing the task, in this case taking a quality blood pressure.

Below is a list of common ABPM machine error codes with solutions:

Error Code	Explanation of Error Code	Solution/Action
LLL	- The batteries need to be replaced	Change the batteries (three AA). 
EC00 EC70 EC90	- The participant is moving too much	- Hold still with the cuffed arm relaxed by your side while the machine is measuring the blood pressure.
EC02 EC42 EC52 EC62	- The hose is kinked - The cuff is not attached properly - There is an air leak - The cuff is not placed properly	- Make sure the hose is not kinked – you may need to disconnect hose from monitor and straighten to ensure no kinks are present and then reconnect hose to monitor. - Check that the hose is tightly connected to the monitor. - Ensure the position of the cuff is in middle of upper arm, the arrow on the cuff is aligned with inside of crease in arm, that the cuff doesn't fall down and that one finger fits under the cuff.  If error codes continue, inform CKiD coordinator and return monitor. Reschedule ABPM monitoring.
EC05 Any other Error Codes	Equipment malfunction	- First try all solution/actions listed above. - If error codes continue, inform CKiD coordinator and return monitor. - Reschedule ABPM monitoring.

17.6 RETURNING ABPM TO ABPM COORDINATING CENTER

When participants are given the ABPM monitor to take home, clinical site staff should provide instructions to them on returning the monitor. **Sites should remind the family of the importance of returning the monitor within a timely fashion so that the monitor can be used by other participants. Also sites should contact the families a couple of days after the visit to remind them to return the monitor.** Monitors can be returned to the ABPM coordinating center by the clinical site or in rare occasions by the participant. **Remember, timing is important!!**

After the ABPM monitoring is completed and the monitor is ready to be shipped back, the coordinator must go to the CKiD website and complete the “On-line Shipping Form” located on the Coordinator’s Corner. Completing the “On-line Shipping Form” alerts the ABPM center that a monitor has been sent back.

17.6.1 Clinical Sites Returning ABPM to ABPM Coordinating Center

Clinical sites should strongly encourage participants to return monitors back to their clinical sites. When a monitor is shipped to a clinical site, the ABPM coordinating center will provide a pre-filled airbill, packaging and “Study Site Instructions” sheet for the site to return the monitor after the participant’s use. The study coordinator should instruct the participant to return the monitor to the clinical center at the end of 24 hours of monitoring. **Once the clinical site receives the monitor, the site should use the return airbill provided and packaging material to ship the monitor back.** In addition to shipping the monitor, diary and participant information sheet, the clinical site should also complete the “On-line Shipping” form in the Coordinator’s Corner on the CKiD website. On the Online Shipping form, check ABPM Monitor Shipment and fill in the following:

- a. Fed Ex #
- b. Participant’s Height
- c. Participant’s Weight
- d. Click the submit button and the ABPM Center will receive an email notifying them of the shipment.

The ABPM Center must have the ABPM visit height and weight to down load the monitor!!!

17.6.2 Participants Returning ABPM directly to ABPM Coordinating Center

Some participants may live several hours away from the clinical site and therefore returning the monitor to the clinical site may be difficult and inconvenient. In these rare cases, the study coordinator should give the participant the “Participant Instructions” sheet, which explains how to ship the monitor to the ABPM coordinating center. The coordinator should complete the shipping form by adding their contact information in the sender fields. The coordinator must provide the site’s address and phone number. The coordinator should also retain the top copy of the FedEx form for their records. It is important that the site has the FedEx tracking number in the event that the monitor is not received by the ABPM Center. Afterwards, the site still must complete “on-line shipping form” when they have confirmation from the parent that the monitor has been sent.

The return airbill will contain the following mailing address:

Lettye Dismukes
CKiD ABPM Coordinating Center
University of Texas Central Lab ABPM
6431 Fannin St, MSB 3.123
Houston, Texas 77030

When scheduling a FedEx pickup, the family should call 1-800-463-3339 and ask to speak with a FedEx representative. Speaking with a FedEx representative ensures that the correct pick-up address is arranged with FedEx. **The family should NOT schedule pick-up using the automated system and package should not be left at a drop box.**

17.7 FEEDBACK TO FAMILIES

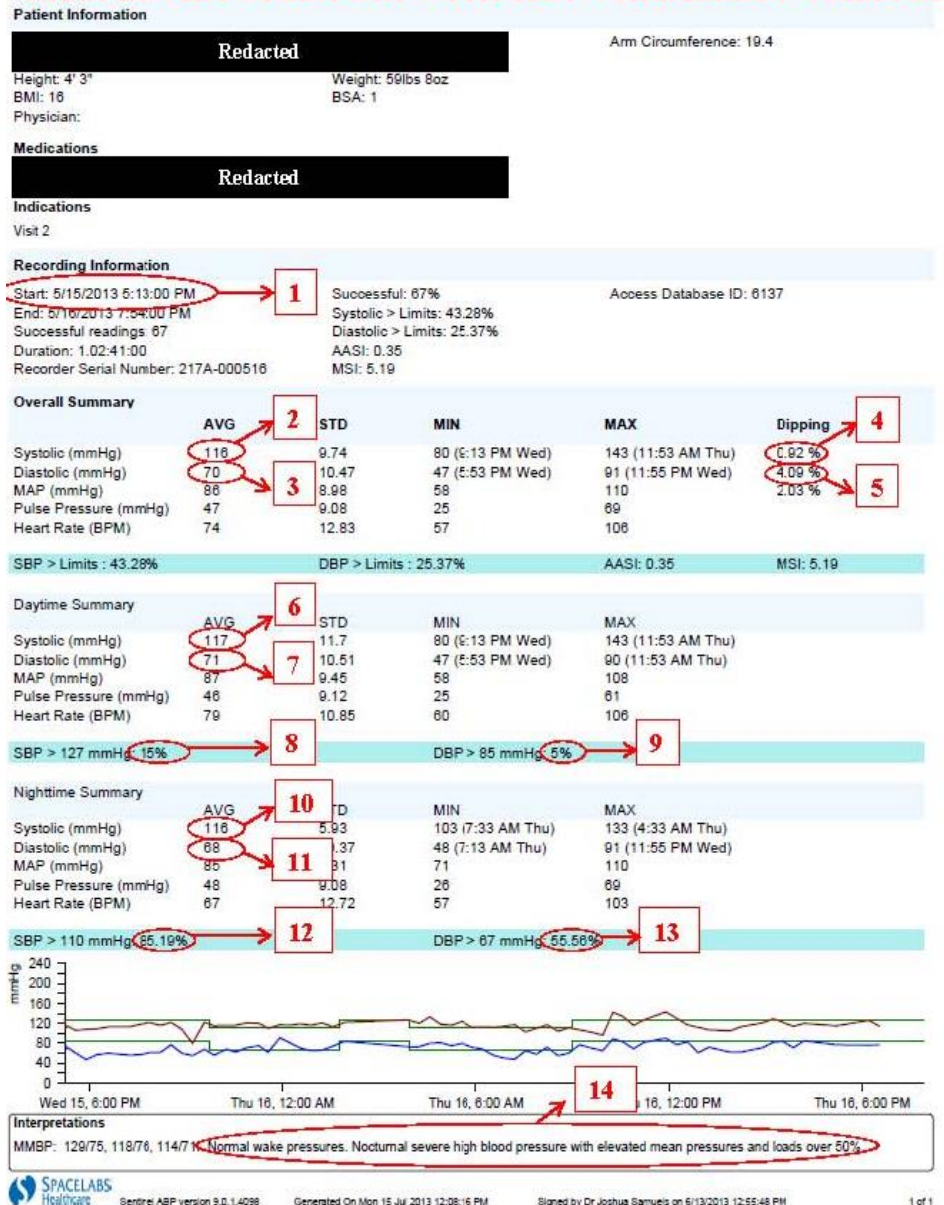
A feedback letter can be provided to the participant's family. Using the ABPM Report with key variables that is provided to the sites by the ABPM Coordinating Center, the site can generate a letter for the family to summarize the ABPM Report. An interactive Online ABPM Report Generator is available on the CKiD website which can be accessed on the "Coordinator Corner's" page, under "ABPM Feedback for Families".

Below is an example of the ABPM Report and feedback letter.

17.7.1 ABPM Report with key variables numbered

1. Date monitor was initialized at the ABPM Center
2. Average systolic for whole day
3. Average diastolic for whole day
4. % systolic sleep decline (dipping)
5. % diastolic sleep decline (dipping)
6. Average systolic while awake
7. Average diastolic while awake
8. % abnormally high systolic while awake
9. % abnormally high diastolic while awake
10. Average systolic while asleep
11. Average diastolic while asleep
12. % abnormally high systolic while asleep
13. % abnormally high diastolic while asleep
14. Interpretation

SAMPLE ABPM REPORT WITH KEY VARIABLES NUMBERED





SAMPLE ABPM REPORT COVER LETTER

To: Parent/ Guardian(s) of [Participant Name]

Date: [mm/dd/yy]

CC: [Nephrologist]

Thank you very much for participating in the Chronic Kidney Disease (CKiD) in Children study. Using what we learn from you in this study, we will be able to help other kids with kidney problems in the future.

One of the goals of this study is to look at how blood pressure might be related to how well the kidneys are working. In the CKiD study, we use ambulatory blood pressure monitoring (ABPM) which provides multiple measurements of blood pressure over a 24-hour period. Since blood pressure can change depending on different circumstances, taking many blood pressure measurements over 24 hours is useful as it gives a better picture of a person's true blood pressure, instead of just relying on one time point. This letter summarizes the attached report from your last ABPM. We encourage you to discuss these results with your physician.

Ambulatory BP results for: [Participant Name]

Date Monitor was initialized at ABPM Center (not date ABPM was worn): [1]

Summary of the whole day:

- The average systolic BP was [2] mmHg for the whole day.
- The average diastolic BP was [3] mmHg for the whole day.
- The systolic BP decreased by [4] % while sleeping.
- The diastolic BP decreased by [5] % while sleeping.

Awake BP Summary:

- The average systolic BP while awake was [6] mmHg.
- The average diastolic BP while awake was [7] mmHg.
- The systolic BP was considered abnormally high [8] % of the time while awake.
- The diastolic BP was considered abnormally high [9] % of the time while awake.

Sleeping BP Summary:

- The average systolic BP while asleep was [10] mmHg.
- The average diastolic BP while asleep was [11] mmHg.
- The systolic BP was considered abnormally high [12] % of the time while asleep.
- The diastolic BP was considered abnormally high [13] % of the time while asleep.

Interpretations: [14] [cut and paste relevant interpretation information from report]

Ambulatory BP Staging Levels in Children (criteria used for CKiD study)

Classification	Clinic BP	Mean Ambulatory BP	BP Load, %
Normal Blood Pressure	< 95th %tile	<95th %tile	<25
White Coat Hypertension	≥ 95th %tile	<95th %tile	<25
Masked Hypertension	< 95th %tile	≥95th %tile	≥25
Pre-Hypertension	≥ 95th %tile	<95th %tile	25-50
Ambulatory Hypertension	≥ 95th %tile	≥95th %tile	25-50
Severe Ambulatory HTN	≥ 95th %tile	≥95th %tile	≥50

Adapted from: Urbina et al, Ambulatory Blood Pressure Monitoring in Children and Adolescents: Recommendations for Standard Assessment Hypertension (2008); 52:433-451; DOI: 10.1161/HYPERTENSIONAHA.108.190329

INFORMATION for ABPM REQUEST

Request must include: Date of visit. KID ID. Visit number.

REQUESTING MONITOR

Complete ABPM Monitor Request form in Coordinator’s Corner on the CKiD website <http://www.statepi.jhsph.edu/ckid/admin/coordinator/coordinator.html>.

* *Form must be completed prior to study visit date*

The ABPM Center will obtain mid-arm circumference measurement from Nephron’s Visit Control Sheet Report. <https://statepiaps.jhsph.edu/nephron/groups/aspproc/>

One week before the ABPM visit, site sends confirmation email to ABPM center to confirm the participant visit.

ABPM Coordinating Center ships monitor to clinical site using FedEx (3 delivery days)

Instructions for the clinical sites:

- Study Coordinator (SC) confirms measurements of arm and reviews instructions with parent/participant
- SC obtains 3 auscultatory (manual) BPs using Mabis Medic kit and records on participant diary
- SC places the ABPM monitor on non dominant arm of participant to take home and obtains first ABPM practice reading
- SC explains the participant diary (WAKE/SLEEP most important) and obtains 2nd ABPM practice reading
- SC provides further explanation (QUICK RETURN) of the monitor and obtains the 3rd ABPM practice

After **24** hours of monitoring

Parent/participant returns the ABPM monitor to the clinical site

Parent/participant ships the ABPM monitor directly to the ABPM center.

* **Site must provide coordinator’s contact information on the FedEx shipping form and site must follow-up with parents to find out when monitor is shipped.**

Clinical site ships the ABPM monitor to the ABPM center

Study Coordinator completes “Online Shipping Form” in the Coordinator’s Corner on the CKiD website.

Once monitor, diary, and Mabis BP data are received at ABPM Center, monitoring will be downloaded and analyzed.

Clinical report will be generated for site and database will be maintained for DCC

ABPM Coordinating Center emails feedback to clinical site coordinator.

17.9 QUESTIONS AND CONTACTS

If you have any questions regarding the process for requesting and/shipping monitors to the ABPM Center or need further information, please use the following contact information below.

ABPM Coordinating Center

E-mail: ABPM@uth.tmc.edu

Lettye Dismukes
ABPM Center

E-mail: Lettye.Dismukes@uth.tmc.edu
Phone: 713-500-5113

Joshua Samuels
Principal Investigator
ABPM Center

E-mail: Joshua.A.Samuels@uth.tmc.edu
Phone: 713-392-1352

Jackie Ndirangu
Project Director
East Coast Clinical Coordinating Center

E-mail: NdiranguJ@email.chop.edu
Phone: 267-426-8388

Julie Starr
Project Director
Midwest Clinical Coordinating Center

E-mail: jwstarr@cmh.edu
Phone: 816-855-1744

Ambulatory Blood Pressure Monitoring Diary

COORDINATOR TO COMPLETE THIS SECTION

CKiD ID:

Monitor SN:

Visit Date:

Return Date:

Cuff size:

Arm (cm): cm Ht (cm):

Age (years): years Wt (kg):

Mabis Medic Blood Pressures:

 #1 #2 #3

Systolic: mmHg

Diastolic: mmHg

Participant To Complete This Section

Date worn: month / day / year

Time went to sleep: : AM/PM
Circle

Time woke up: : AM/PM
Circle

SLEEP TIME *WAKE TIME*

are very important for the analysis of your blood pressure

Participant Activity and Medications Diary:

Time <small>Circle</small>	Description	Meds Taken
10:20 AM/PM	Took Meds (example)	1,3,4
: AM/PM		
: AM/PM		
: AM/PM		
: AM/PM		
: AM/PM		
: AM/PM		
: AM/PM		
: AM/PM		
: AM/PM		
: AM/PM		
: AM/PM		
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: AM/PM		

Participant To Complete This Section

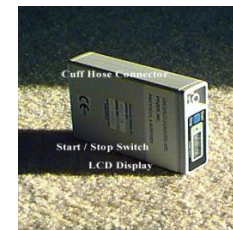
	Medication Name	Dose	Schedule
Ex:	Lisinopril	5 mg	2 x day
#1:			
#2:			
#3:			
#4:			
#5:			
#6:			
#7:			
#8:			
#9:			

No medications taken



**24 hour
Ambulatory Blood
Pressure Monitoring
(ABPM)**

What to do when you get home with
the Ambulatory Blood Pressure
Monitor



**Please try to complete the 24 hr
Blood Pressure Monitoring directly
after your CKiD visit or by:**



Monitor Features

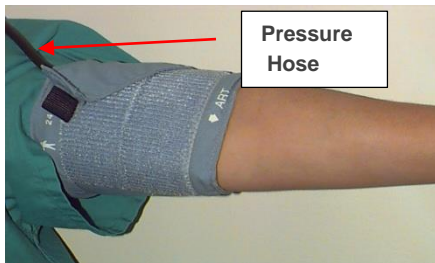
Blue Start / Stop switch - used for manually starting a BP reading

Black On /Off switch - used to power on or power off the monitor.

Cuff hose connector - the tube to the arm cuff attaches here using finger tight pressure. No tools are needed.

Placement and Usage

1. Place the cuff on the non-dominant arm with the artery arrow aimed pointed down at the interior of the elbow. The illustration below is a good example of proper cuff placement. **The cuff should be tight enough so it doesn't fall down but loose enough that one finger fits under cuff.**



Note: Make sure that the cuff velcro has at least 3 inches of overlap and the pressure hose is exiting at the top of the cuff.

Placement and Usage (cont'd)

2. Place pressure hose up through your shirt sleeve then down toward your waist where you can attach to the monitor.
3. Connect the pressure hose to the fitting on the monitor by pushing the hose until you hear the metal connector click. Check that the hose is connected correctly, by gently tugging on the metal connector.
4. Either fasten with a belt or place the monitor in a pocket.

Example of Proper Monitor Placement 5



5. Turn the monitor on. (Black switch on the side of the monitor)
6. Rest/relax the arm with the Blood Pressure Cuff to your side. **The monitor will not take a reading if the arm is bent, above the heart, or holding a heavy object.**

7. The monitor takes a blood pressure reading every **20 minutes for 24 hours**. Note: You **will not see the readings**.
8. **After the 24 hour monitoring is completed, turn the monitor off and place it back in the brown cardboard box.**
9. **Follow the instructions provided by your coordinator on how to return the monitor.**

IMPORTANT REMINDERS

- The monitor CANNOT get Wet.
- Remove the Monitor when swimming, playing contact sports (like football), outside in inclement weather (when outdoors), etc.
- At night, place the monitor box to the side of your bed.
- The monitor should still be on and recording your Blood Pressure while sleeping.
- Complete the diary and send it back with the monitor

***DO NOT GIVE TO PARTICIPANT IF SITE IS RETURNING MONITOR!**

PARTICIPANT INSTRUCTIONS

DO NOT THROW AWAY ANY OF THE PACKAGING OR BOX! YOU WILL NEED IT TO RETURN ABPM!

READ INSTRUCTIONS CAREFULLY!

CALL STUDY SITE IF YOU HAVE ANY QUESTIONS.

1. Leave return airbill and bubble wrap in box. Set aside until monitor is ready to be returned to ABPM Coordinating Center.
2. When monitor is ready to be returned to ABPM Coordinating Center, take bubble wrap and return airbill out of box.
3. Make sure monitor is turned off. Disconnect BP cuff hose from monitor. Place monitor in holster and wrap in bubble wrap.
4. Place wrapped monitor, BP cuff and filled out diary sheet in middle of box with at least 2 inches of packing peanuts underneath. Cover items with rest of packing peanuts.
5. Tape box closed with proper shipping tape. Fill out only the date on the airbill.
6. Peel backing off airbill and affix to side of box.
7. Call 1-800-463-3339 and schedule courier pickup. Because of insurance reasons this box must be picked up by a courier. Do not leave at drop box! To ensure the courier picks up the monitor from the correct location, speak with a FedEx representative to arrange pick-up. DO NOT schedule pick-up using the automated system.
8. Call study site once box has been picked up.

Contact information

Site Coordinator: _____

Site Phone Number: (_____) _____ - _____

STUDY SITE INSTRUCTIONS

PLEASE READ UPON OPENING!

DO NOT THROW AWAY ANY OF THE SHIPPING MATERIAL OR BOX!

YOU WILL NEED IT TO RETURN ABPM!

If Study Site is Returning ABPM:

1. Pull monitor, BP cuff and diary out of box for study visit. Leave shipping instructions, return airbill, clear packing sleeve and bubble wrap in box. Set aside until monitor is ready to be returned to ABPM Coordinating Center.
2. When monitor is ready to be returned to ABPM Coordinating Center, take bubble wrap, clear packing sleeve and return airbill out of box.
3. Make sure monitor is turned off and wrap in bubble wrap.
4. Place wrapped monitor, BP cuff and diary in box. Cover with packing peanuts.
5. Tape box closed with proper shipping tape. Fill out the “sender” fields on the return airbill and keep top sheet noted “Sender’s Copy.”
6. Place rest of airbill in clear packing sleeve.
7. Peel backing off sleeve and affix to side of box. Peel off small white strip and fold end of sleeve over adhesive strip to seal packing sleeve.
8. Call 1-800-463-3339 and schedule courier pickup. To ensure the courier picks up the monitor from the correct location, speak with a FedEx representative to arrange pick-up. **DO NOT schedule pick-up using the automated system.**
9. Go to Coordinator’s Corner on the CKiD website. Select online shipping form. Fill out sender’s email, site # and site name at top of form. Select ABPM shipment at bottom of form and fill out FedEx tracking number, participant’s height and weight. Click submit.

If Participant is Returning ABPM:

1. Pull monitor, BP cuff and diary out of box for study visit. Leave participant shipping instructions, return airbill, clear packing sleeve and bubble wrap in box.
2. Place monitor on pt and emphasize importance of timely return of ABPM monitor to ABPM Coordinating Center.
3. Complete the shipping form by adding the site's contact information in the senders fields. You must provide the site's address and phone. You should retain the top copy of the FedEx form for your records. It is important that the site has the FedEx tracking number in the event that the monitor is not received by the ABPM center.
4. Read over enclosed instruction sheet with pt on how to ship ABPM and make sure they have a clear understanding of what is required. Give pt box with instructions, packing material and return airbill inside of it.
5. Call pt on day monitor is supposed to be returned to verify that it has been/will be shipped and to answer any questions the pt may have. If pt will be scheduling a courier pick-up, remind them to speak with a FedEx representative to ensure the correct pick-up location is provided to the courier.
6. Go to Coordinator's Corner on the CKiD website. Select online shipping form. Fill out sender's email, site # and site name at top of form. Select ABPM shipment at bottom of form and fill out FedEx tracking number, participant's height and weight. Click submit.

Contact information

ABPM Coordinating Center

ABPM@uth.tmc.edu

Lettye Dismukes

Lettye.Dismukes@uth.tmc.edu

713-500-5113

Fax: 713-500-5680

Dr. Joshua Samuels

Joshua.A.Samuels@uth.tmc.edu

713-392-1352

University of Texas Medical School at Houston

6431 Fannin St, MSB 3.123

Houston, TX 77030

Coordinator's ABPM Cheat Sheet

Coordinator's General Tasks

During the visit, place the ABPM monitor on the participant and take 3 practice readings with the ABPM machine (steps 7, 9 & 10 below). Proper placement and education is critical for achieving successful participant compliance with a 24 hour ABPM. These 3 practice readings serve to test the monitor, obtain baseline information, and familiarize the participant to the functioning of the monitor. In the rare event that the participant is not wearing the monitor home from the visit, these 3 ABPM practice readings should still be obtained during the study visit and the monitor turned off before sending it home with the family. The participant should also be instructed to wear the ABPM and complete the 24hr monitoring within a week of the visit.

Complete the upper left section of the diary before sending the ABPM home with the participant. The arm circumference, age, height and weight of the participant should be recorded. The CKiD study Mabis Medic BPs (auscultatory BP) should also be recorded. **Do not record ABPM practice readings or Dinamap (i.e., BPs taken by any automated machine) on the diary.** The medication list may also be filled out to assist the family.

Record your name and address as the "sender" on the return Fed Ex slip even if the participant is returning the monitor via Fed Ex. This is vital for maintaining confidentiality of the participant. Also, record the Fed Ex tracking number on the return slip for your records. When the family returns the monitor to you or you are aware that they have sent it via Fed Ex, **complete an electronic shipping form on the CKiD website** (Coordinator's Corner). Include the Fed ex tracking number and participant's height and weight on this electronic shipping form.

ABPM Placement and Instruction

1. The ABPM Center will send the proper cuff based on the arm measurement taken at the previous visit. On the day of visit, confirm mid arm circumference measurement and compare it to the cuff size received from the ABPM Center (ranges are on the cuff itself). In some instances, two cuffs will be sent if the participant's mid arm circumference falls between two cuff sizes, or if the study coordinator requests two cuff sizes via the comments section of the ABPM Monitor request form. Always choose the largest cuff size that can be used as an undersized cuff typically produces an elevated blood pressure reading.
2. Place cuff on non-dominant arm with artery arrow pointed down at the interior of the elbow.
Demonstrate placement and note that the cuff should be tight enough so it doesn't fall down but loose enough that one finger fits under cuff.



Note: Ensure that the cuff velcro has at least 3 inches of overlap and the pressure hose is exiting at the top of the cuff.

3. Place the hose up through the participant's shirt sleeve then down toward his/her waist where you can attach to the monitor.
Show how to secure hose to prevent kinking.
4. Connect the pressure hose to the fitting on the monitor by pushing the hose until you hear the metal connector click. Verify that the hose is connected correctly, by gently tugging on the metal connector.
Demonstrate how to connect and disconnect hose.

5. Fasten monitor with a belt or place the monitor in a deep pocket.
Demonstrate how to secure monitor
6. Turn the monitor on. This is the black switch on the side of the monitor.
Demonstrate how to turn monitor on and off. Explain that the monitor should be worn for 24 consecutive hours. It should be turned off and removed for a bath/shower, swimming or other vigorous activity such as contact sports that may harm the machine. The monitor should be worn during a 24 hour period in which there is limited time that the monitor must be turned off.
7. **Press the Blue Start / Stop button to begin the first ABPM practice reading.**
Show the participant how the monitor counts down from 5 and then pressurizes the cuff. Note the cuff pressure in the LCD window and explain to the participant that this will be visible only until the fourth reading has been taken.
8. Review the importance of diary recordings.
Emphasize the need to record the time the participant goes to sleep, the time they wake up (even if they are lounging in bed for a while after waking up), and the time(s) any medications were taken.
9. **Press the Blue Start / Stop button again and take your second ABPM practice reading.**
*Instruct the participant to limit activity during the reading, such as relaxing the arm at their side, to allow the monitor to do its task. The monitor will not take the reading if the arm is bent, above the heart, or holding a heavy object. Explain that the monitor takes a blood pressure reading every 20 minutes for a total of 24 hours and **they will not see the reading!***
10. Address any questions the participant might have, review the instructions one more time, then **press the Blue Start / Stop button and take the third practice ABPM reading (all other readings will be automatic for the remainder of the 24hrs).**
11. Ensure the participant has the diary, site contact numbers, instruction sheet for the return of the monitor, and understands the basic instructions for ABPM monitoring and return.
Review the instruction sheet for returning the monitor and stress the need to return as soon as possible or within 1-2 weeks of visit.

Key points to remember

- It's important that the ABPM be worn for a full 24 hour consecutive period.
- If the monitor is removed for > one hour, add the time that it was removed to the end of the 24 hrs.
 - Suggest participant to choose a time when the monitor would only need to be off for 1 hour or less.
 - If too many consecutive hours are missed, we will not be able to analyze the data.
- Blood pressure readings while sleeping may be the most important.
- The monitor will take a reading every 20 minutes. During the day it will beep to alert you when it is about to take a reading. (Note: There will not be a beep during night hours, between 8pm-8am).
- When the cuff inflates, the participant's arm should be relaxed and still.
- After blood pressure is taken, a single soft beep indicates that the BP was taken correctly. If there are several quick beeps, then an error has occurred and the machine will try again in 3 minutes.
- For alarms: check to be sure that the arrow is placed in front over the elbow, the cuff is not too loose or too tight, the tubing is not kinked or disconnected.
- At night, place the monitor box to the side of the bed. Place the monitor under a pillow to muffle the noise.
- On the diary page, it is important to record: sleep and wake times, time medications were taken
- At the end of the 24 hour period, the monitor should be turned off with the black ON/OFF switch and returned as quickly as possible so others may use the monitor.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 18: MONITOR HANDLING AND TRANSMISSION OF DATA

18.1 ABPM COORDINATING CENTER HANDLING OF MONITOR AFTER RETURN

Once the ABPM monitor is received at the ABPM coordinating center, the following steps are taken to complete the monitoring download and ensure proper data assignment:

1. The monitor is attached to the computer via a serial cable and the data is downloaded.
2. An initial assessment is made as to the quality of the monitoring. If the quality is deemed acceptable further data entry is performed in preparation for statistical analysis. If the monitoring is deemed unacceptable the data will be saved in an accessory database so that the data is not lost but it will not be imported into the main CKiD database. The unacceptability of the monitoring will be communicated to the patient center via email or phone as necessary and a repeat monitoring scheduled.
3. The patient demographic information from the DCC is matched to the monitor utilizing the monitoring id and the monitor serial number as documented by the scheduling database.
4. The KID ID, height, weight, age, birthdate, and race are entered into the SpaceLabs ABPRMS program.
5. The patient medications are entered into the medications section of the SpaceLabs ABPRMS program.
6. The patient wake and sleep times as reported by the patient are entered into the SpaceLabs ABPRMS program. In the event no wake and sleep times are reported, the times are estimated based on heart rate criteria and error patterns.
7. Utilizing an export function within the SpaceLabs software, the downloaded monitoring data is exported in an ASCII format. This export prepares the data for import into the statistical database.

At this point the monitor download is completed, all information is saved on a secure network data drive, and there are multiple copies of the data to ensure that the monitoring will not have to be repeated. The monitor will be reprogrammed and sent to the next center requesting a monitoring.

18.2 DATA WORKUP AND ANALYSIS

Our data import and analysis process utilizes proprietary software written primarily in Visual Basic within the Microsoft Access 2002 environment. Primary attributes of this software are:

1. The ability to define and analyze multiple sleep / nap periods.
2. The automatic determination of pediatric blood pressure limits. These limits can be defined as Task Force 1987, Working Group Update, or limits as determined by the German Task Force (Soergel et al) study addressing ambulatory limits.
3. The ability to export a complete ABPM analysis report and graph in a pdf file format that can be emailed as an attachment.

4. The ability to generate other statistical datapoints such as area under and over the curve, blood pressure index, coefficient of variability, load, and correlation to activity levels (if a parallel actigraphy study is performed).

This database is located on a secure network drive and all data backup is performed dynamically.

18.3 DATA FORMAT AND DELIVERY

Data will be delivered to the DCC on a monthly basis in a comma delimited ascii file format as a default. However, it should be noted that many other formats are easily possible including but not limited to tab delimited, Access data table, and dbf formats.

The data variables will be transmitted in the order of the ABPM Lab Codebook, encrypted, zipped into a password protected file and emailed to the DCC. It is important to note that edits to old files will be sent in a separate email.

18.4 REPORT TO INDIVIDUAL CLINICAL SITE

A clinical report of the results of the monitoring will be provided to each site by email with a goal reporting time of one week from receipt of the monitor.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 19: ECHO

19.1 OVERVIEW

This section describes the echocardiographic procedures that are to be performed on children participating in CKiD. Echocardiographs will be performed by standard M-mode and Doppler echocardiography. The echocardiogram and Doppler studies will be performed on all children beginning at Visit 2 and every four (4) years thereafter.

Cardiovascular Imaging Core Research Laboratory for “CKiD” Study

- **Directions:**
- **CD-ROM: PC compatible**
- **Format: PowerPoint with AVI clips**
- **AVI clip format windows media player**
- **Review paper copy of notes pages included with CD-ROM**

A CD-ROM of these slides has been sent to the sonographers at each site, and includes moving images of example echocardiograms. This instructional CD-ROM is PC-compatible. Double click the power point presentation on the CD-ROM to open it. To view the program appropriately, click “slide show” (under “View”, in the upper left screen). Once in the slide show, press enter to advance to the next slide. To run video clips you will need the upgraded version of Windows Media Player. This is a free download if you presently use Windows Media Player. If the slides with AVI clips show an image then go blank you do not have the required program to open the file and will need to download the program from the website. Go to website: <http://windowsmedia.com/9series/Download/download.asp>. Please call the Cardiovascular Imaging Core Research Lab (CICRL) if you need assistance viewing the instructional CD-ROM.

Overview of Qualification for Site Sonographer and CKiD Participant

QUALIFICATION OF SITE PRIMARY SONOGRAPHER

Primary sonographer provides qualification ECHO.

- Sonographer's qualification echo includes 12 CKiD protocol images.
- Sonographer completes "Sonographer Qualification Worksheet"



Cardiovascular Imaging Core Research Lab (CICRL) reviews sonographer's qualification ECHO and certifies site to perform echos.



Certified site primary sonographers can train other site sonographers.



ASE BASELINE ECHOCARDIOGRAM OF CKiD PARTICIPANT'S IMAGES

Site sonographer MUST submit an American Society of Echocardiography (ASE) baseline ECHO for each CKiD participant.

- The ASE baseline ECHO:
 - should be obtained at the child's first CKiD ECHO visit (e.g. visit 2, 6...).
 - includes **standard images** to rule out structural heart disease.
 - is performed in conjunction with the 12 CKiD protocol images.
- Sonographer completes "CKiD Sonographer ECHO Worksheet." On the worksheet, under Visit Type, site must circle "ASE Baseline ECHO" and the appropriate visit number.
- Sonographer also completes "Sonographer Self-Critique form" and must check "ASE Baseline ECHO" and the appropriate visit number.
 - For example, if the child did not have an echo at visit 2 and the first echo is obtained at Visit 6, then the sonographer should check "ASE Baseline ECHO" and "visit 6". This will indicate the child's first echo was obtained at visit 6.



POST - QUALIFICATION OF CKiD PARTICIPANT'S IMAGES

After the subject's ASE Baseline ECHO is submitted, sonographer only obtains the 12 CKiD protocol images at all future visits.

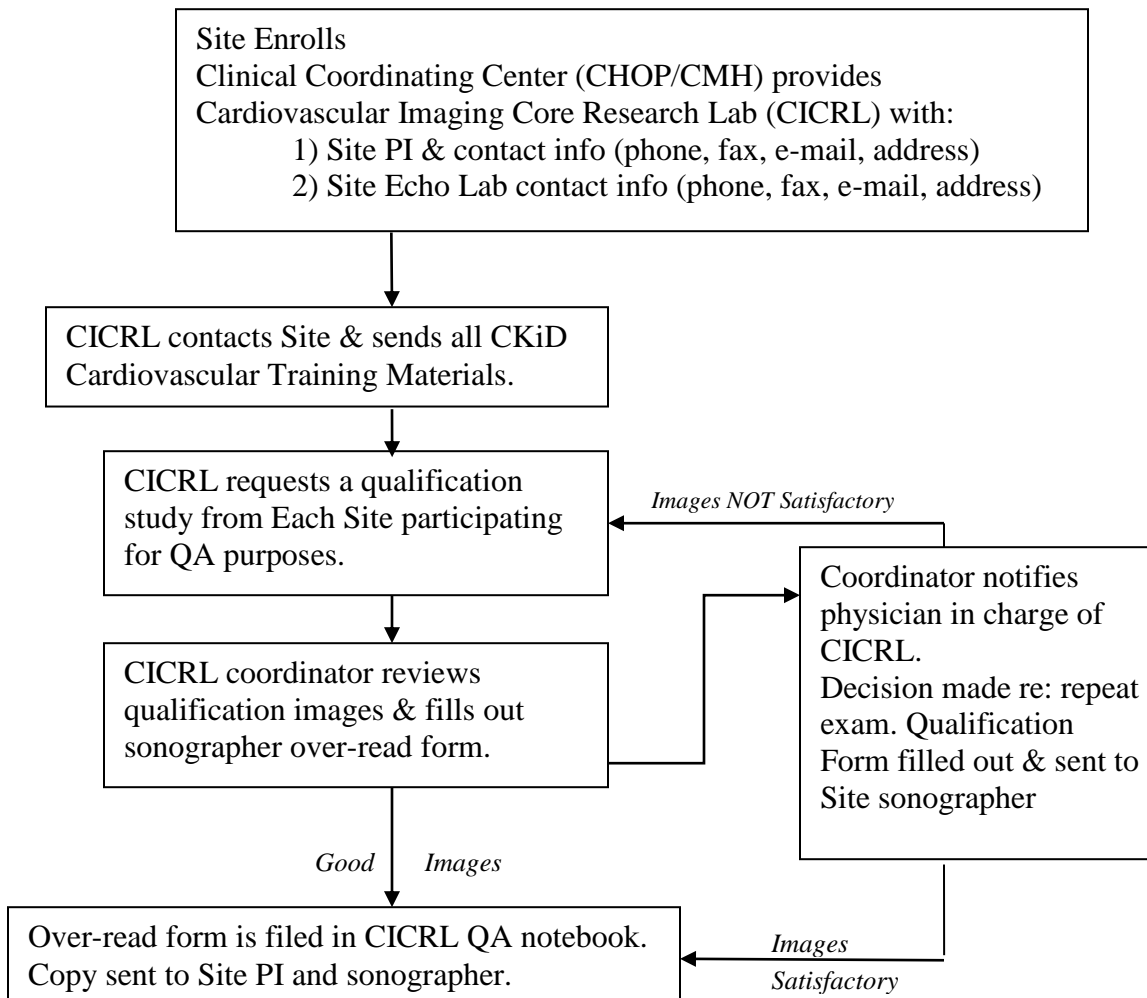
- For these visits, the "CKiD Sonographer ECHO Worksheet" and "Sonographer Self-Critique form" should indicate 12 CKiD protocol images only, and check the appropriate visit number.

19.2 QUALIFYING SITE PRIMARY SONOGRAPHER

Qualifying Primary Sonographer

- The Primary Sonographer will provide CICRL with a qualification Echo study, along with sonographer identification and contact information. (Only one sonographer at each site provides the qualification study.)
- All sites have been provided with appropriate & adequate training materials to comply with data & image acquisition.

19.2.1 Site Sonographer Qualification Study Flow Chart



19.3 Study guideline reference sheet for all CKiD visits

The first CKiD Echo Visit (which is the 12 image protocol study) must be accompanied with a COMPLETE ASE guideline baseline ECHO. The ASE baseline echo will be reviewed by Dr. Michael Taylor to determine if the subject has any structural heart disease and subject's eligibility for future ECHOs. The CICRL will email an ALERT form (to the PI and study Coordinator) if the subject is NOT eligible to obtain future ECHOs. The complete ASE baseline echo is for research purposes only and is not clinically read by the CICRL.

It is the responsibility of the site to disseminate "*clinical*" information.

After the initial complete ASE echo is sent in (along with the 12 CKiD image protocol) all other ECHO visits for that subject will only require the 12 CKiD image protocol along with the subject's worksheet and critique form completely filled out.

Points to remember:

1. The first CKiD echo visit for the CKiD participant needs **a complete ASE baseline Echo and the 12 CKiD protocol images.**
2. All visits after the first echo visit (e.g. Visit 6), only require the 12 CKiD protocol images.
3. The two (2) forms (worksheet and critique form) must be completed for every visit.
4. Site must ensure the that the appropriate data is on CD/ videotape
 - CKiD Study
 - Patient ID number (KID)
 - Clinical Site ID number
 - Visit number
 - Date of study
5. **Do NOT ZOOM** the LV or AO/LA m-mode
6. Acquire at least 10 COMPLETE cycles of each image (CICRL will measure 3 consecutive cycles).
7. Acquire the High Parasternal Aortic SAX view ZOOMED, be careful not to acquire the base of the Aorta (please refer to training materials).

19.4 CKiD Sonographer ECHO Worksheet and Sonographer Self-Critique Form

19.4.1 CKiD Sonographer Echo Worksheet

Clinical Site #: _____

Subject ID #: _____

Sonographer Initials: _____

Date of Study: _____

ASE Baseline Echo: Yes No

Regular Study Visit:

V2

V6

V10

V14

Irregular (Accelerated) Visit ____

Post RRT Study Visits:

DV1b

DV2

DV3

DV4

DV5

Irregular (Accelerated) Visit ____

TV2

TV4

ASE Baseline Echo:

If this is the first CKiD echo visit for the participant, then check "yes" and indicate the appropriate visit number. (A complete ASE guideline baseline ECHO and the 12 CKiD images must be sent.)

Is this a Repeat Echo? Yes No

Sonographer Checklist

Check When Echo Study Completed

1. _____ All of the above worksheet data filled in.
2. _____ Subject ID and site number entered correctly on tape/disk (no patient name is to be listed on tape/disk or worksheet)
3. _____ Complete Echo performed to exclude the presence of congenital heart disease (**ONLY for 1st Echo**).
4. _____ Echocardiographic CKiD study complete. (10 cardiac cycles per image, sweep speed 100mm/sec)
 - a) _____ Parasternal Long-Axis Image (**Image #1**)
 - b) _____ PLAX 2D-guided M-Mode of LV (**Image #2**)
 - c) _____ PLAX 2D-guided M-Mode of LA and Aorta (**Image #3**)
 - d) _____ 2D-parasternal short-axis image (papillary muscle level) (**Image #4**)
 - e) _____ 2D Apical 4-chamber image (**Image #5**)
 - f) _____ 2D Apical 2-chamber image (**Image #6**)
 - g) _____ Mitral Inflow Pulse Wave Doppler (**Image #7**)
 - h) _____ Pulse Wave Tissue Doppler Imaging
 - 1) _____ Medial mitral annulus (**Image #8**)
 - 2) _____ Lateral mitral annulus (**Image #9**)
 - i) _____ Suprasternal notch (high parasternal) short axis image of the aorta (**Image #10**)
 - j) _____ Suprasternal notch (high parasternal) short axis image of the aorta – ZOOMED (**Image #11**)
 - k) _____ Suprasternal notch (high parasternal) short axis image of the aorta-2D guided M-Mode of Zoomed image (**Image #12**)
4. _____ "Alert" protocol followed (if applicable). "Alert" Finding (specify): _____
5. _____ Videotape/disc copied and stored. Both tapes/discs labeled with clinical site, patient ID and study date.

Shipment Directions for CKiD Sonographer:

- Make a copy of this form. Keep a copy for CKiD records. Mail original form with the Sonographer Self Critique Form and tape/disc to:

CCHMC

Attn: Lauren Longshore Brown

Cardiology Dept., ML 2003

3333 Burnet Ave.

Cincinnati, OH 45229

513-803-5517

Lauren.Longshore@cchmc.org

FedEx Slip:

- **Contact your CCC for a FedEx slip (if needed) and it will be emailed to you.**

CKiD Sonographer Self Critique Form

Clinical Site ID: ____ Sonographer Initials: ____ Is this the Primary Sonographer: Yes No

Subject ID #: _____ CKiD exam date: _____

ASE baseline ECHO: Yes No

Is this a Repeat Echo? Yes No

Regular Study Visit:
 V2
 V6
 V10
 V14
 Irregular (Accelerated) Visit ____

Post RRT Study Visits:
 DV1b TV2
 DV2 TV4
 DV3
 DV4
 DV5
 Irregular (Accelerated) Visit ____

Directions: The CKiD Sonographer will fill out the information below.

	Circle YES or NO	
1. Is the subject ID displayed correctly on the image?	Yes	No
2. Did the Sonographer fill out the Echo Worksheet?	Yes	No
3. Were all images appropriately recorded?	Yes	No
4. Was overall gain set appropriately?	Yes	No
5. Was the TGC set appropriately?	Yes	No
6. Was the depth set appropriately?	Yes	No
7. Did the Sonographer indicate any "alert" parameters on the Echo Worksheet?	Yes	No
8. Did the patient have good acoustic windows for data acquisition? If no, please comment.	Yes	No
Comments		

Directions for CKiD Sonographer:

- Make a copy of this form. Keep a copy for your records. Mail original form with the Sonographer Echo Worksheet and Videotape/CD to:
CCHMC
Attn: Lauren Longshore Brown
Cardiology Dept., ML 2003
3333 Burnet Ave.
Cincinnati, OH 45229
513-803-5517
Lauren.Longshore@cchmc.org

FedEx slip:

- Contact your CCC for a FedEx slip (if needed) and it will be emailed to you.

Periodically, the CIRCL will email the following site survey form to obtain current information for site sonographers.

SITE SURVERY FORM

Staff Information

Site Name _____

Site Number _____

<i>Sonographers # 1</i>	
Name	
email	
Dept Address	
Phone	
Fax	

<i>Sonographers # 2</i>	
Name	
email	
Dept Address	
Phone	
Fax	

<i>Site study Coordinator</i>	
Name	
email	
Dept Address	
Phone	
Fax	

19.5 OBJECTIVES OF ECHOCARDIOGRAPHY IN THE CKiD STUDY

Cardiovascular Imaging Core Research Laboratory for “CKiD” Study

- **Demonstration of the Echocardiogram Exam for CKiD patients**
- **Objectives**
 - Develop a working knowledge of technical exam components for exam accuracy
 - Develop understanding of correct tissue Doppler technique
 - Develop understanding of aortic distensibility imaging technique
 - Understand how to document the exam for independent review & analysis by Core Lab

Patient Set-Up

Cardiovascular Imaging Core Research Laboratory for “CKiD” Study

- **The following information should be entered via the keyboard, displayed on the screen and recorded on the videotape/CD**
 - Patient’s CKiD identification number
 - Date of the study
 - Sonographer initials
 - CKiD center number

Video Tape/CD Preparation

Video Tape/CD Preparation

- One echo study/patient per tape
- Each tape should be labeled with:
 - the study name (CKiD)
 - clinical site ID number
 - patient ID number
 - visit number
 - date of study

Patient Preparation

Patient Preparation

- Enter CKiD SONOGRAPHER Worksheet & enter required data information.

Patient Preparation & Positioning

- Explain the purpose of procedure & stress that it is painless.
- Attach a disposable ECG lead to each of the ECG cords. Peel off the backing and apply to the subject:
 - Black goes to LEFT arm or shoulder
 - White goes to RIGHT arm or shoulder
 - Red goes to ABDOMEN to the far right of the umbilicus below the right costophrenic angle.
 - Adjust the size and position of the ECG tracing on the monitor using the knobs on the control panel located above the keyboard.
 - THE R WAVE SHOULD BE TWICE AS HIGH AS THE T WAVE. DO NOT MAKE COMPLEX TOO SMALL.
- Subject in supine, left lateral decubitus position on an exam table with the drop out portion of the mattress removed from the bed, if available. The left forearm of the patient is positioned under his/her head and the right arm resting on the right hip.

2D and M-Mode Acquisition General Principles

2-D & M-mode Image Acquisition General Principles

- **To rule out structural heart disease a standard baseline echocardiogram is performed in a slightly darkened room with a transducer appropriate for the patient**
- **Most shallow depth possible should be utilized**
- **Minimum of 10 beats recorded for each acquisition**
- **M-mode obtained at a 100 mm/s sweep speed**

A standard baseline echocardiogram should follow the Intersocietal Commission for the Accreditation of Echo Labs (ICAEL) standards. A complete description of the echo exam can be found at: www.ICAEL.org. Click on The Standards, then click on Pediatric Transthoracic and scroll to section 3, pages 3-5.

- **Sequence for acquiring echo data**
 - **Standard baseline Echocardiogram is first performed using ICAEL standards and recorded on Super VHS/CD.**
 - **Images for CKiD study are to be performed separately, after the standard echo and on the same VHS tape/CD.**

Echo Gain Settings

2-D & M-mode Image Acquisition Appropriate Gain Settings

It has been noted that optimal definition of endocardial & epicardial interfaces for making measurements at the Core Lab require using slightly higher gain than is generally optimal for displaying these interfaces on the video monitor during performance of the study.

The necessity for using higher gain to record images of the LV is emphasized so that optimal recordings for interpretation at the Cardiovascular Imaging Core Research Lab (CICRL) are obtained.

Echocardiographic Examination

CKiD Echocardiographic Exam

- **The following images are examples of the minimum requirements by the Cardiovascular Imaging Core Research Lab for analysis of the echocardiograms.**
- **The echocardiogram may need to be repeated if the study does not meet these requirements.**

Measurement Information for Local Sites

CKiD Echocardiographic Exam Measurements

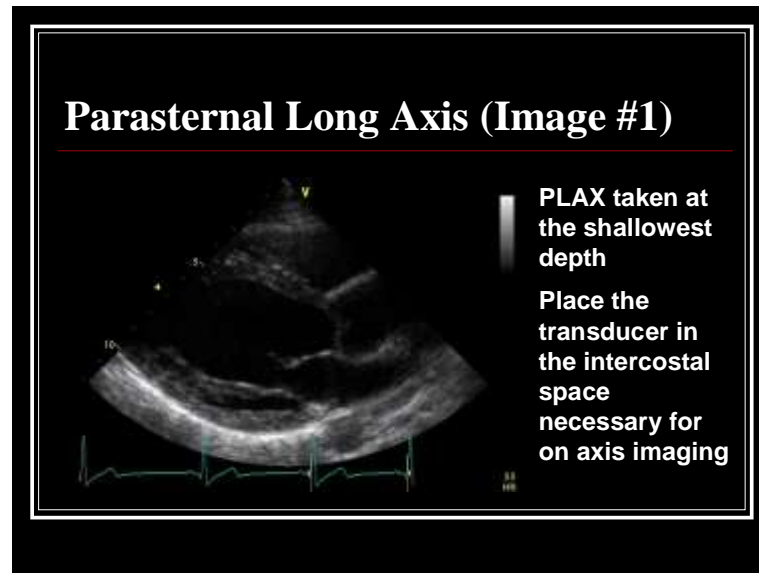
- Local sites sonographers/physicians are **NOT** to make measurements on the tape or supply to CICRL
 - Local site clinical reports (if generated) should **NOT** be forwarded to the CICRL
- All CKiD echo measurements will be performed by the CICRL**

CKiD Research Images

CKiD Research Images

- All of the following echocardiographic images are necessary for completion of the CKiD study.
- Total of 12 CKiD ECHO research images

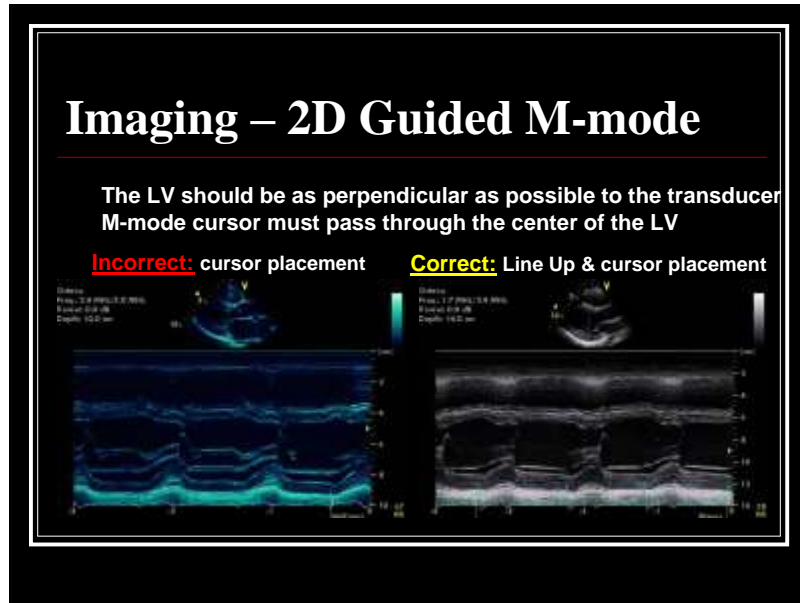
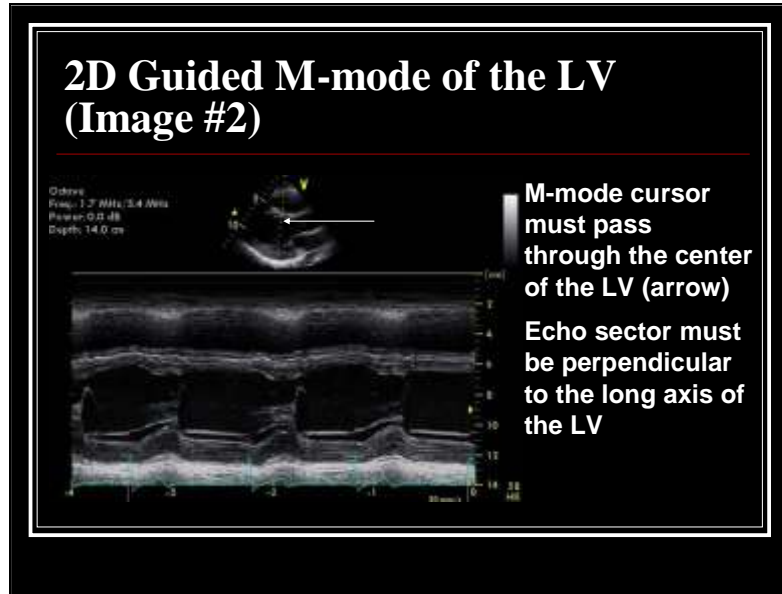
Parasternal Long Axis



In an ideal long axis image the scan lines are perpendicular to the LV septum and posterior wall, the TV chordae and the MV leaflet short posterior chordae are delineated, the LV septal tendons are identified and the QRS on the ECG tracing is clearly evident.

In general, when imaging the heart in the PLAX view, one should attempt to adjust the transducer position such that the aorta is not angulated at its junction with the LV. Then, the transducer position should be adjusted to record the maximum anterior-posterior aspect of the LV. Record 10 cardiac cycles of a 2-D image from the parasternal view. Remember to maximize the LV size by panning medially and laterally, and clarify LV interfaces, to obtain an ideal long-axis image. The selection of transducer frequency and focal length can influence endocardial definition. An inadequate parasternal long axis view with the LV walls not perpendicular to the scan lines will not meet CICRL requirements for adequate measurement. Care should be taken to avoid being too low or too high on the patient's chest so that images which result in rounding of the apex and or foreshortening of the ventricle are not recorded. If this occurs, try to move one interspace higher or lower. As a general rule, imaging should be performed with the highest frequency transducer that provides adequate penetration of the chest for good structural (especially endocardial) definition.

M-Mode Study Protocol



Above, please note the emphasis on the correct cursor placement within the LV to ensure good septal and posterior wall endocardial visualization avoiding the mitral valve apparatus.

To measure the LV minor axis dimension and parietal thickness accurately with M-mode technique it is necessary to orient the echocardiographic beam from the parasternal window to pass perpendicularly through the interventricular septum and posterolateral LV wall at the level of the junction of the papillary muscle tips and mitral chordae. This should be performed under two-dimensional guidance.

For accurate and reproducible measurement of these structures, dominant lines representing the necessary interfaces (the right and left sides of the septum and the endocardial and epicardial surfaces of the posterior LV wall) should exhibit continuous motion in the correct pattern from the structure for at least 10 cardiac cycles. M-mode tracing of the left ventricle will be recorded at a speed of 100 mm/sec simultaneously with the ECG.

The CICRL personnel will measure 3 consecutive beats of the septum, LV and LV posterior wall at end-diastole and end-systole using the leading edge to leading edge method. Assessment of the left ventricular systolic function will be performed by calculating the shortening fraction, mid wall systolic thickness (MWST) and mid wall shortening (%) by averaging three cardiac cycles which will be entered in a data base format and utilizing the following formulas:

Shortening fraction formula (%):

$$\frac{LVIDd - LVIDs}{LVIDd} \times 100$$

Mid wall systolic thickness (MWST)

$$\left[(LVIDd + IVSd / 2 + LVPWd / 2)^3 - (LVIDd)^3 + (LVIDs)^3 \right]^{0.33333} - LVIDs$$

Mid wall shortening(%)

$$\frac{\left[(LVIDd + LVPWd / 2 + IVSd / 2) - LVIDs - MWST \right]}{(LVIDd + LVPWd / 2 + IVSd / 2)} \times 100$$

LVPWd = left ventricle posterior wall end-diastole

IVSd = interventricular septum end-diastole

LVIDs = left ventricle end-systolic dimension

LVIDd = left ventricle end diastolic dimension

The left ventricular M-Mode mass will be calculated by averaging three cardiac cycles which will be entered in a data base format and utilizing the following formula as described by the American Society of Echocardiography:

1. M-mode LV mass

➤ Use the measurements obtain from the LV study preset

➤ **LV mass formula:**

$$0.832\{(IVSd + LVPWd + LVIDd)^3 - LVIDd^3\} + 0.6$$

Left ventricular mass will be indexed by dividing by the height raised to the power of 2.7 (LVMI).

This approach to indexing has been demonstrated to best account for body habitus. LVH will be defined as LVMI >/= 95th percentile for normal controls.

LV Geometry

In addition to LVMI, relative wall thickness (RWT) will be calculated to assess LV geometric patterns. Calculation of the left ventricular RWT will be done by averaging three cardiac cycles utilizing the following formula which will be entered in a data base format.

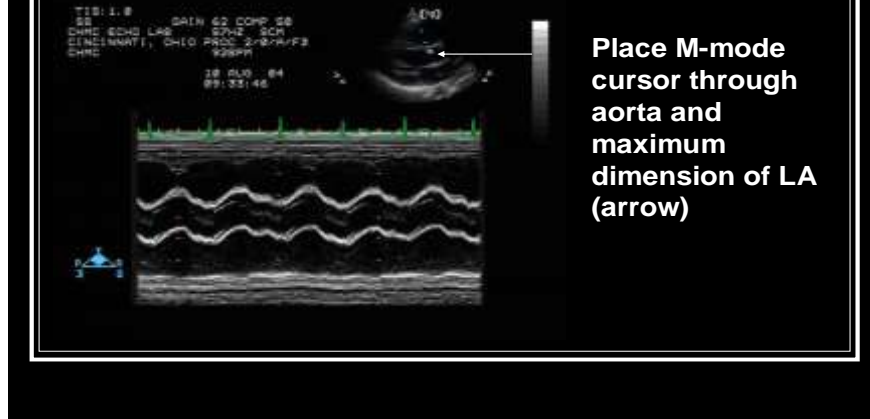
2. M-mode relative wall thickness (RWT)

➤ **RWT formula:**
$$\frac{LVPWd + IVSd}{LVIDd}$$

An increase in LV mass is classified as concentric hypertrophy if the RWT is >.041 and eccentric hypertrophy when RWT is <0.40. If the RWT is increased, but the LV mass is <0.40, the patient is considered to have concentric LV hypertrophy.

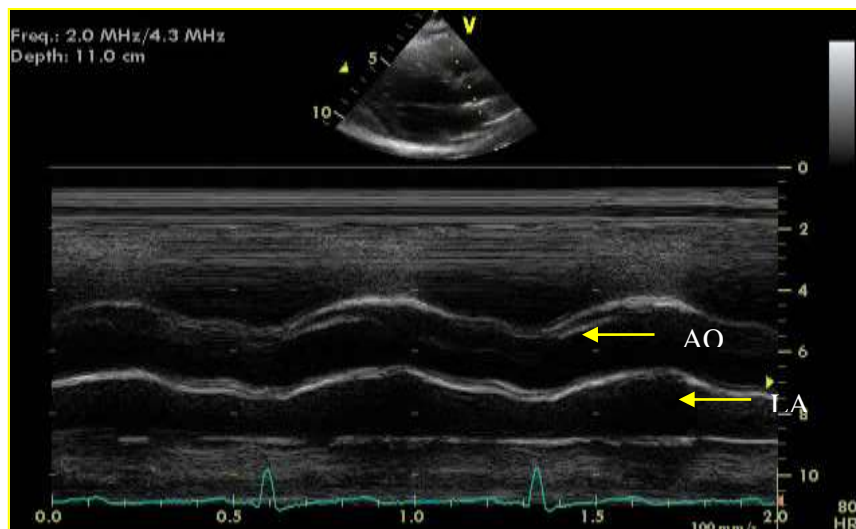
<i>Geometry</i>	<i>Mass</i>	<i>Relative Wall Thickness</i>
<i>Normal</i>	Normal	Normal
<i>Concentric Remodeling</i>	Normal	Increased
<i>Eccentric Hypertrophy</i>	Increased	Normal
<i>Concentric Hypertrophy</i>	Increased	Increased

2D Guided M-mode of the AO & LA (Image #3)



The M-mode cursor should be positioned perpendicular through the aorta and the maximum dimension of the LA. The sonographer should display the two-dimensional update image on the screen with the M-mode image of the aorta and LA. The sonographer should record 10 cardiac cycles at a sweep speed of 100 mm/sec.

The CICRL personnel will measure 3 consecutive beats of the aorta and left atrium. The aorta will be measured at end-diastole and the left atrium at end-systole using the leading edge to leading edge method. Left atrial size will be determined and indexed by height to adjust for differences in body size.

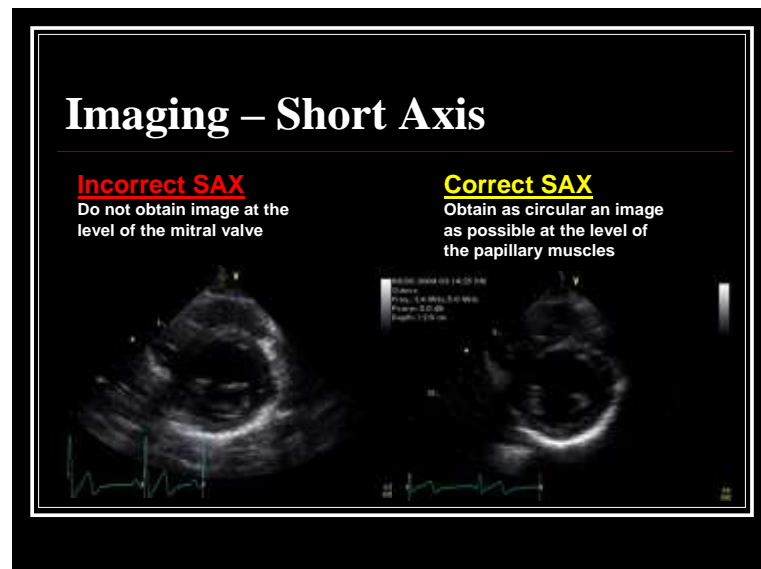


Parasternal Short Axis



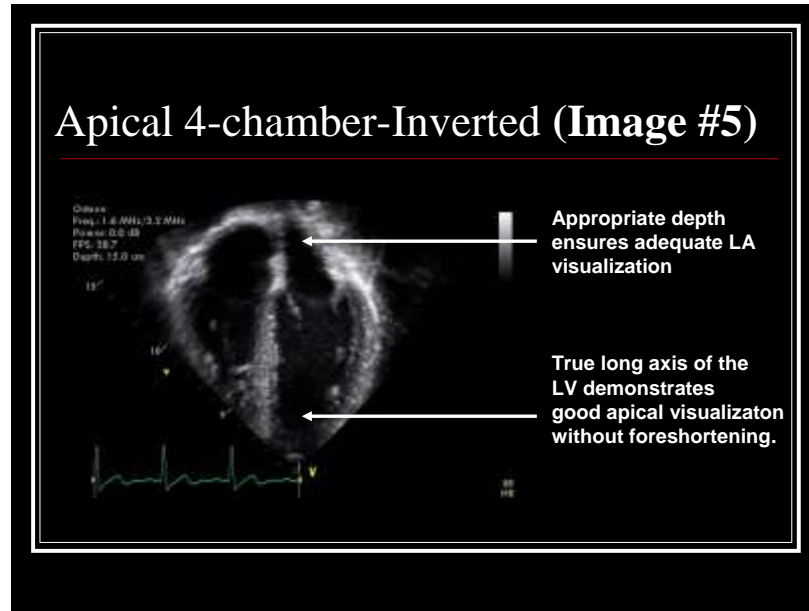
Record 10 cardiac cycles in the parasternal short axis view. When imaging in the PSAX, it is important to obtain as circular an image of the LV as possible, directing the transducer inferior to the mitral valve where the mitral valve motion is lost or where there is only minimal excursion of the leaflets.

PSAX view which appears elliptical or egg-shaped indicate that the echo sector has intersected the LV in an oblique fashion instead of perpendicular to the long-axis.



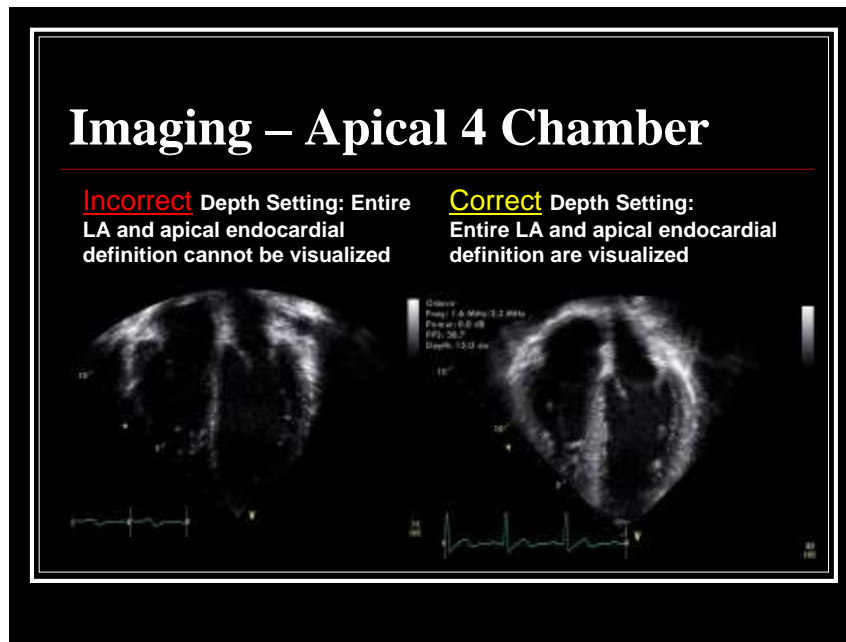
The image on the left is recorded too superior in the left ventricle capturing the mitral apparatus. The image on the right is more distal and at the appropriate papillary muscle level of the LV.

Apical 4-Chamber View

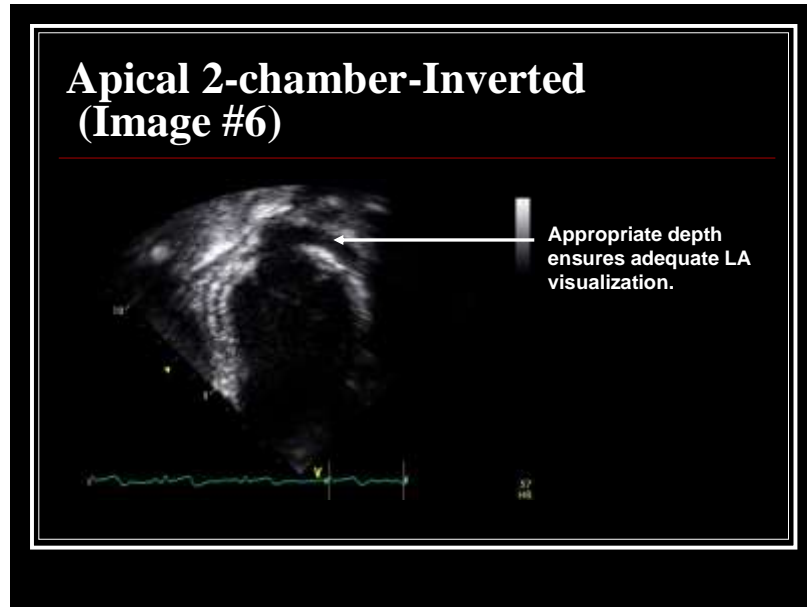


Record 10 cardiac cycles of the apical 4 chamber view. The sonographer should make every attempt to display the true long axis of the LV, avoiding “foreshortening” of the chambers. Adequate apical visualization may require higher gain settings. From this view, good endocardial visualization is necessary for the CICRL to derive adequate and correct data.

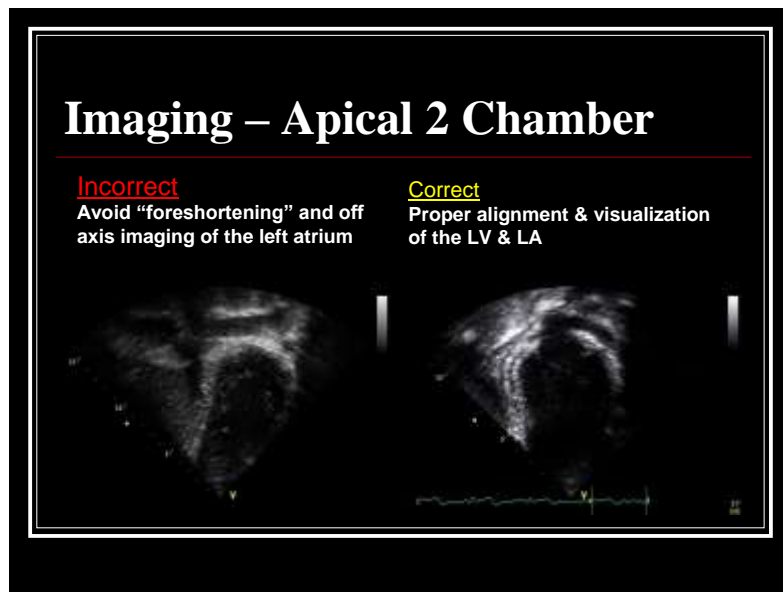
In addition, appropriate depth should be used to ensure that the entire LA is well visualized.



Apical 2 Chamber Image



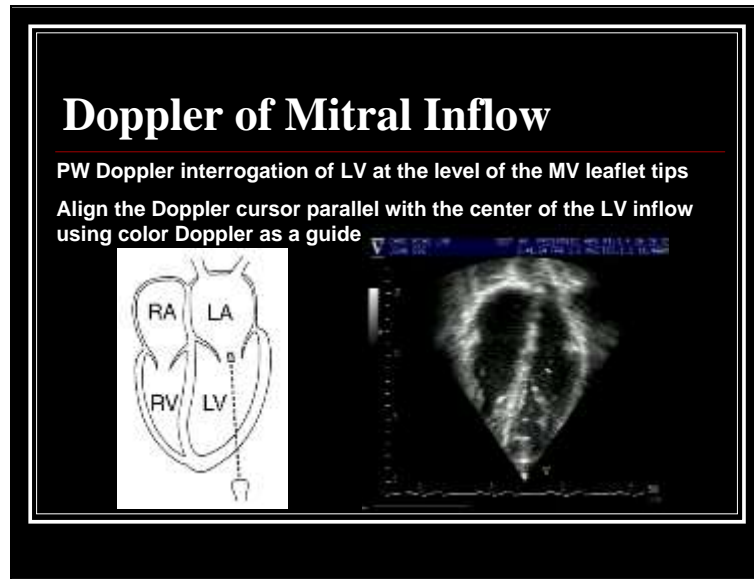
The 2 chamber view is needed to evaluate the left atrium. Therefore, it also requires appropriate depth settings to view the left atrium in its entirety. Record at least 10 cardiac cycles of the apical 2-chamber.



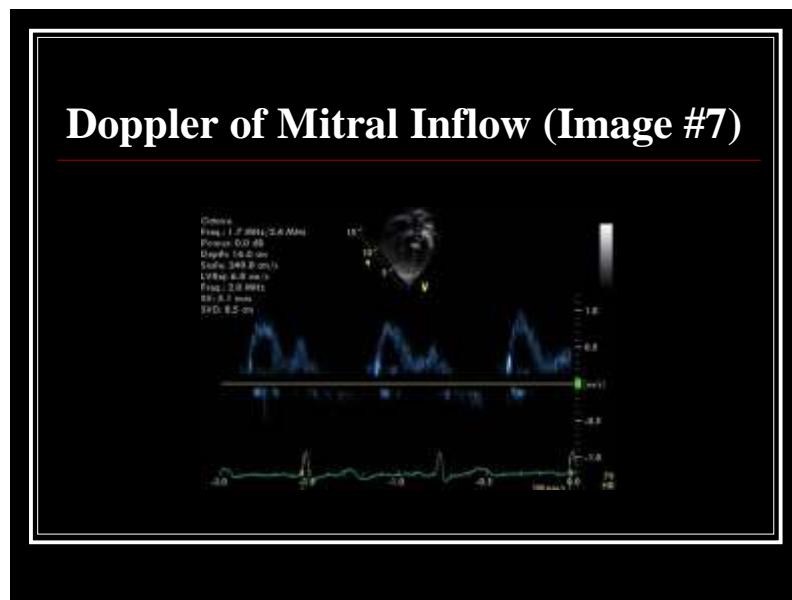
Left Atrial Volume Measurement

The CICRL will evaluate 3 consecutive cardiac cycles for left atrial volumes. Two-dimensional echo images are obtained in both the apical 4 and 2 chamber views. The outline of the atrial endocardium and length of the chamber is traced in both the 4 and 2 chamber views, at end-systole. When the inner surface of the coapted mitral valve leaflets does not form a straight line, a line joining the attachment of the leaflets to the annulus is taken as the atrial outline. The atrial appendage and pulmonary veins, when visualized, are excluded from outlines. The length of the atrium is drawn as the maximum length perpendicular to the mitral annulus. A biplane volume will then be calculated using modified Simpson’s rule.

Mitral Inflow Acquisition



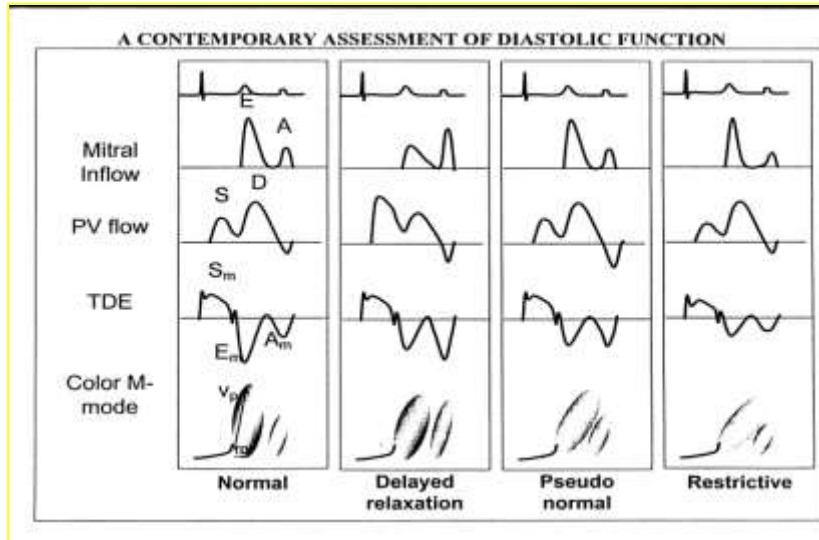
Pulsed Doppler recording of transmitral flow velocity should be performed from the apical four-chamber view with the sample volume (1-2 mm) positioned parallel to the direction of inflow at the tips of the mitral leaflets during diastole. This view may be slightly leftward from the traditional two-dimensional apical 4-chamber view (e.g left image in above Figure).



The sonographer should display the 2-dimensional update image on the screen with the Doppler recording of transmitral flow velocity. Record 10 cardiac cycles at a sweep speed of 100 mm/sec. Record mitral flows demonstrating the highest peak velocities and most narrow spectral dispersion.

Mitral Inflow Measurements

CICRL personnel will measure 3 consecutive beats in the apical 4 chamber image of the mitral inflow Doppler pattern. The goal is to use Doppler echocardiography for the assessment of ventricular filling for the analysis of diastolic function. Left ventricular diastolic dysfunction is thought to be an important cause of cardiac morbidity and appears to be one of the earliest detectable cardiovascular abnormalities in a variety of disease states. The diagram below demonstrates the changes occurring in mitral valve Doppler velocities with progressive diastolic dysfunction.

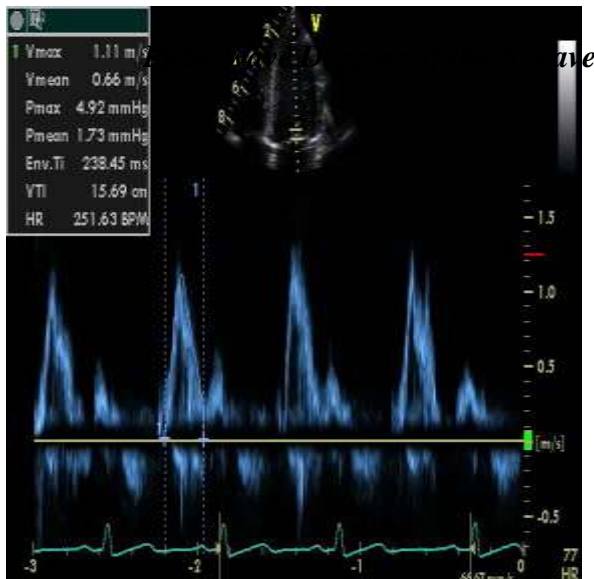


Mitral Valve (MV) Inflow

1. Mitral E-wave & A-wave measurements

Measure 3 consecutive beats of the E and A peak velocities

E = E wave of MV inflow, **A** = A wave of MV inflow

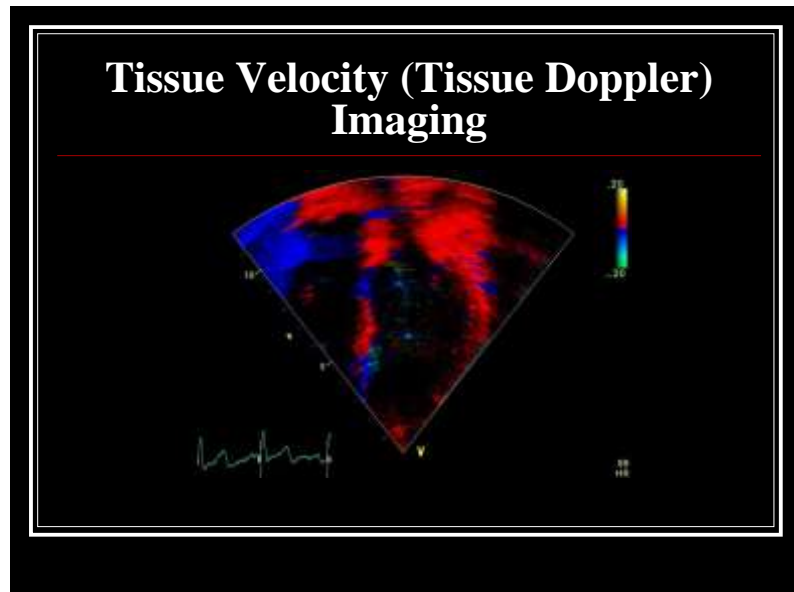


Measurement of Pulse-wave Doppler of the E-wave



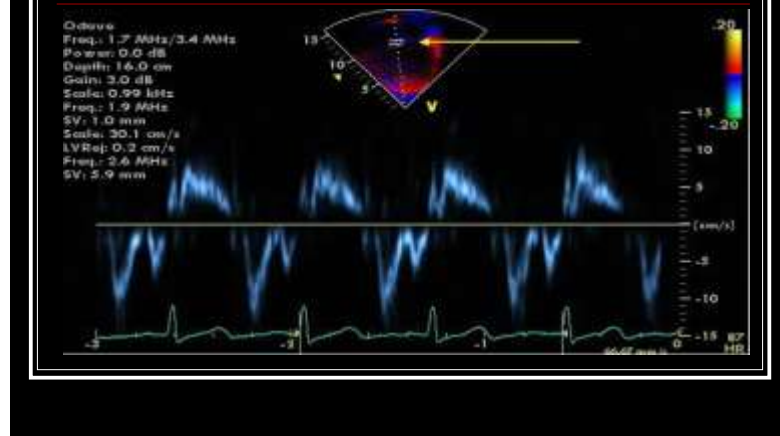
Measurement of Pulse-wave Doppler of the A-wave

Tissue Doppler Imaging



Acceptable tissue Doppler imaging (TDI) requires the acquisition of an appropriate, on-axis apical image as previously described. Use predetermined settings for TDI if available. If pre-sets are not available, decrease PW Doppler gain, use velocity filters to obtain low frequency signals and scale to include systolic and diastolic velocities. The image should not be foreshortened. The apex of the heart should occupy the apex of the sector. This is the standard 4-chamber view with the crux of the heart, mitral and tricuspid valves shown. TDI provides velocity information only in the beam direction.

Tissue Doppler Image of Medial Mitral Annulus (Image #8)

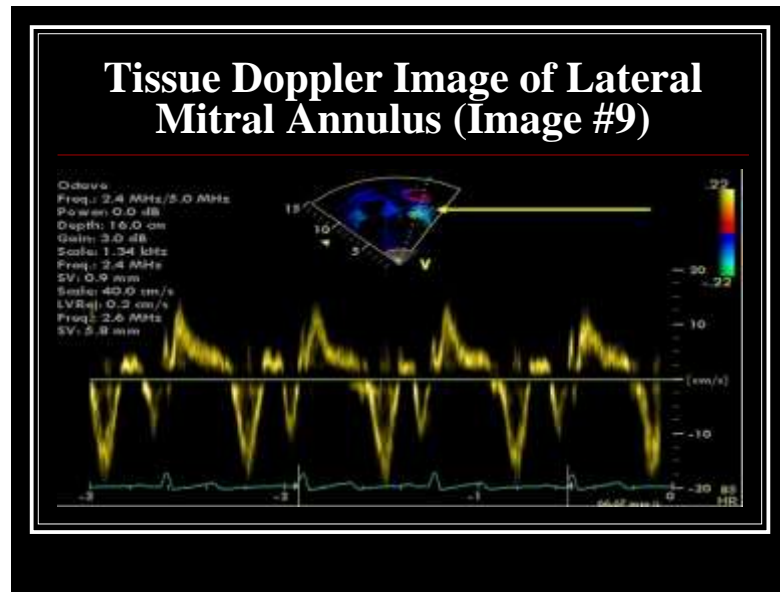


Pulsed Tissue Doppler recordings should be obtained at both the lateral and medial base of the LV (i.e. at the mitral annulus) by placing the Doppler sample volume at the respected sites in the apical four-chamber view. An attempt should be made to record beats demonstrating the highest peak velocities and narrowest spectral dispersion. The sonographer should display the 2-D update image on the screen with the Doppler recording of myocardial tissue velocity recorded at 100 mm/sec with 10 cardiac cycles recorded. Successful TDI will be demonstrated by obtaining characteristic wave pattern of myocardial tissue velocities: forward systolic wave, an early diastolic myocardial velocity and an atrial contraction signal.

The Doppler velocity scale, gain settings and baseline should be appropriately set to allow COMPLETE visualization of the Doppler spectral waveforms accurately showing the peak velocities in both diastole and systole. Cutting the tips off the Doppler pattern, or setting the gains too high causing difficulty in determining true velocity, will now allow the CICRL to accurately measure data.

The above image shows the Doppler sample volume placed at the medial annulus.

The CICRL will measure 3 consecutive cardiac cycle TDI wave forms, measuring the Em, Am, and the Sm velocities at the medial and lateral mitral valve annulus.



Doppler sample volume placed at the lateral annulus of the mitral valve.

The Doppler velocity scale, gain settings and baseline should be appropriately set to allow COMPLETE visualization of the Doppler spectral waveforms accurately showing the peak velocities in both diastole and systole. Cutting the tips off the Doppler pattern, or setting the gains too high causing difficulty in determining true velocity, will now allow the CICRL to accurately measure data.

The sonographer should display the 2-D update image on the screen with the Doppler recording of myocardial tissue velocity recorded at 100 mm/sec with 10 cardiac cycles recorded.

Aortic Compliance Image Acquisition

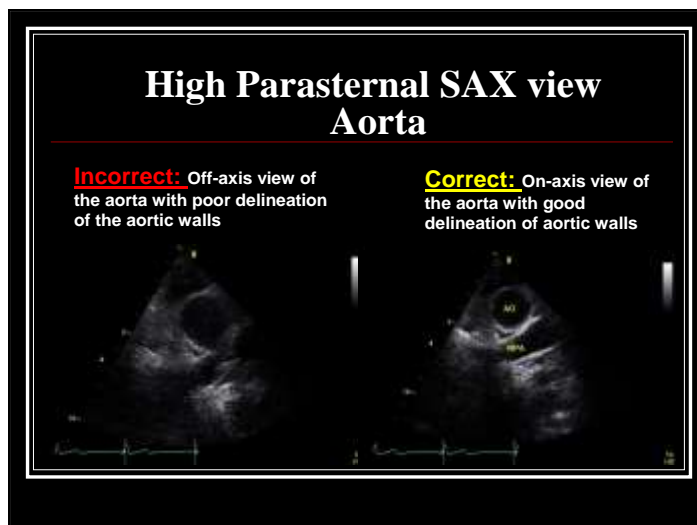
Aortic compliance refers to the ability of the aorta to distend relative to a given pressure. It is an index of regional aortic stiffness.

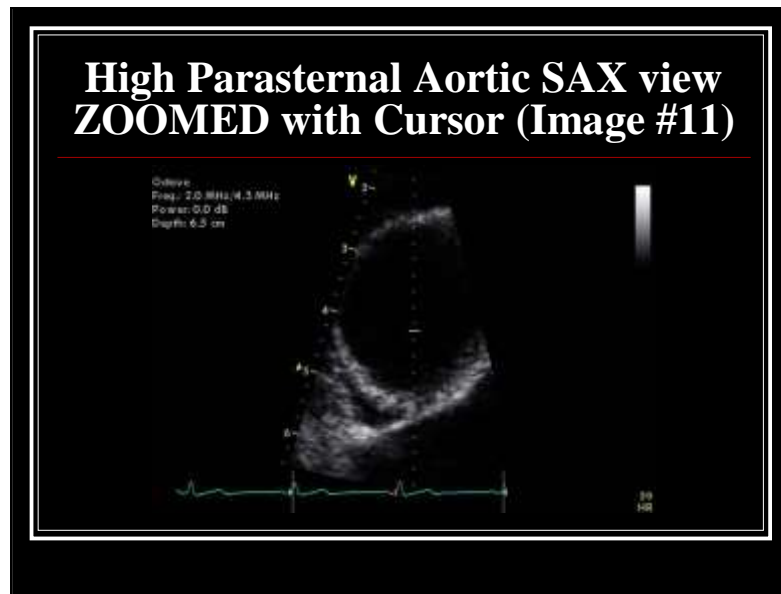


Thoracic aorta at the level of the ascending aorta as it crosses the RPA in the high parasternal short axis view. Aortic short axis view should be obtained from the high parasternal view. Assure on-axis images by obtaining a circular aortic view. Appropriate gain setting to allow accurate determination of the aortic walls is essential.

Provide 10 consecutive cardiac cycles of the thoracic ascending aorta in its transverse axis as it crosses the right pulmonary artery.

The aorta should be circular or near circular at this level.





Zoomed image of the thoracic aorta at the level of the ascending aorta as it crosses the RPA at high parasternal short-axis view with M-mode cursor.

Cursor placement should be in the center of the thoracic aorta at the level of the ascending aorta as it crosses the RPA.

Provide 10 consecutive cardiac cycles of the thoracic ascending aorta in its transverse axis as it crosses the right pulmonary artery.

The aorta should be circular or near circular at this level.



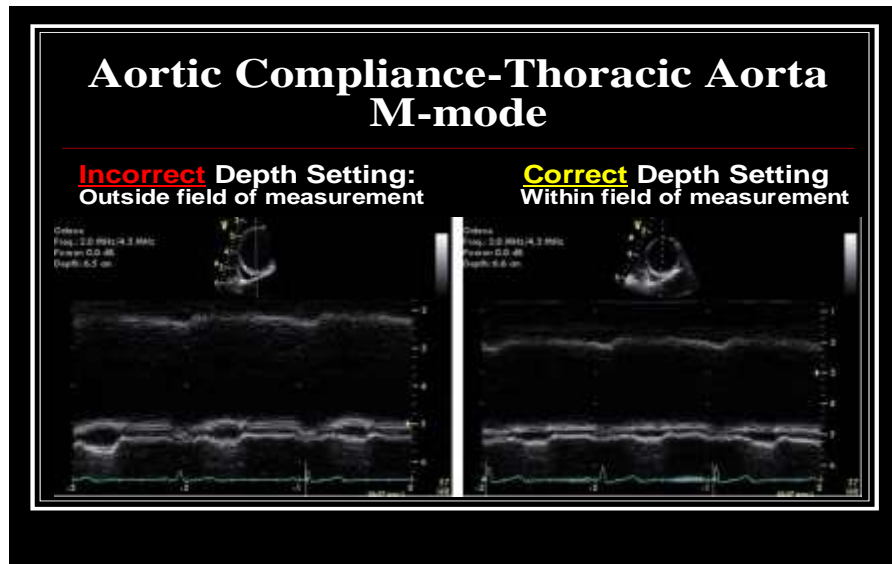
2D guided M-mode transthoracic echocardiography of the aortic root at the high parasternal short-axis view with a simultaneous electrocardiogram recording.

Assure appropriate gain and depth setting to completely visualize both the anterior and posterior walls of the aorta.

Provide 10 consecutive cardiac cycles of the thoracic ascending aorta in its transverse axis as it crosses the right pulmonary artery.

The aorta should be circular or near circular at this level.

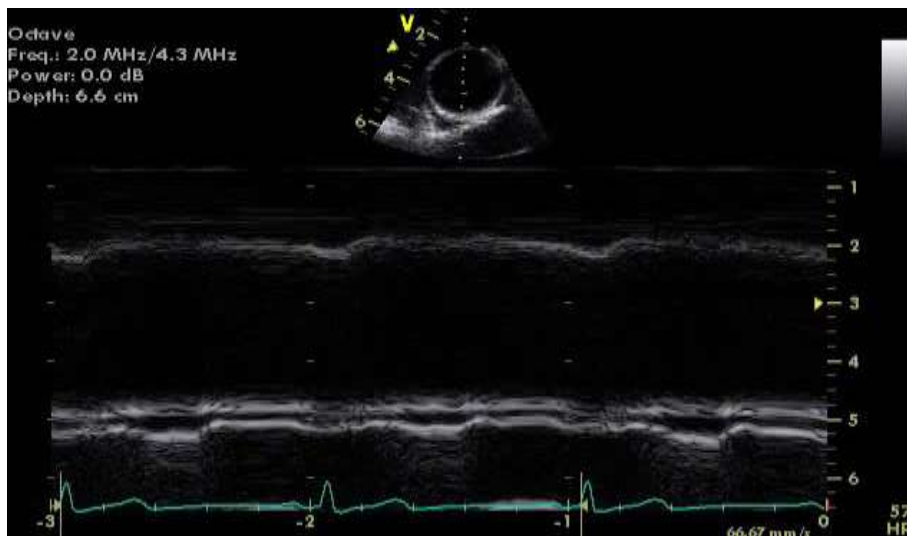
19.6 AORTIC COMPLIANCE IMAGE MEASUREMENTS



Parameters to be measured by the CICRL

The following parameters will be measured by the CICRL from 3 consecutive cardiac cycles of the cross-sectional echocardiographic image of the aorta.

- Thoracic aorta compliance (mm/m^2) will be measured by the CICRL at the level of the ascending aorta as it crosses the RPA by two-dimensional guided M-mode transthoracic echocardiography of the aortic root at high parasternal short-axis view (see below).



- Aortic sysSystolic diameter (**AoS**) will be measured by the CICRL at the time of full opening of the aortic valve, and diastolic (**AoD**) diameter at the peak of the QRS complex at the simultaneous electrocardiogram recording.

Echocardiographic Calculations

The following indexes of aortic function will be calculated by the CICRL:

Aortic strain (AS)

➤ **Aortic strain formula:**

$$100 \left(\frac{AoS - AoD}{AoD} \right)$$

Aortic root distensibility

➤ **Aortic root distensibility formula:**

$$2 \left(\frac{AoS - AoD}{AoD \times PP} \right) (cm^2 \times dyn^{(-1)} \times 10^{(-6)})$$

PP = pulse pressure

Aortic stiffness index

➤ **Aortic stiffness formula:**

$$\ln \left(\frac{SBP}{DBP} \right) \left(\frac{AoS - AoD}{AoD} \right)$$

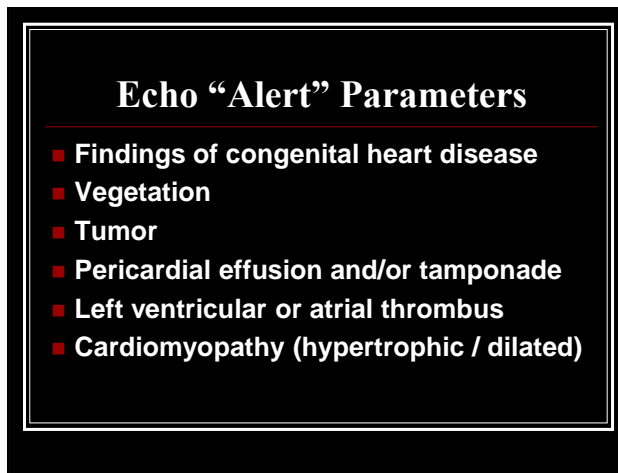
SBP = systolic blood pressure,
DBP = diastolic blood pressure

Aortic pressure strain modulus (Ep)

➤ **Aortic pressure strain modulus formula:**

$$\frac{PP}{\left[\left(\frac{AoS - AoD}{Aod} \right) \right]} (cm^2 \times dyn^{(-1)} \times 10^{(-6)})$$

19.7 ECHO ALERT PARAMETERS

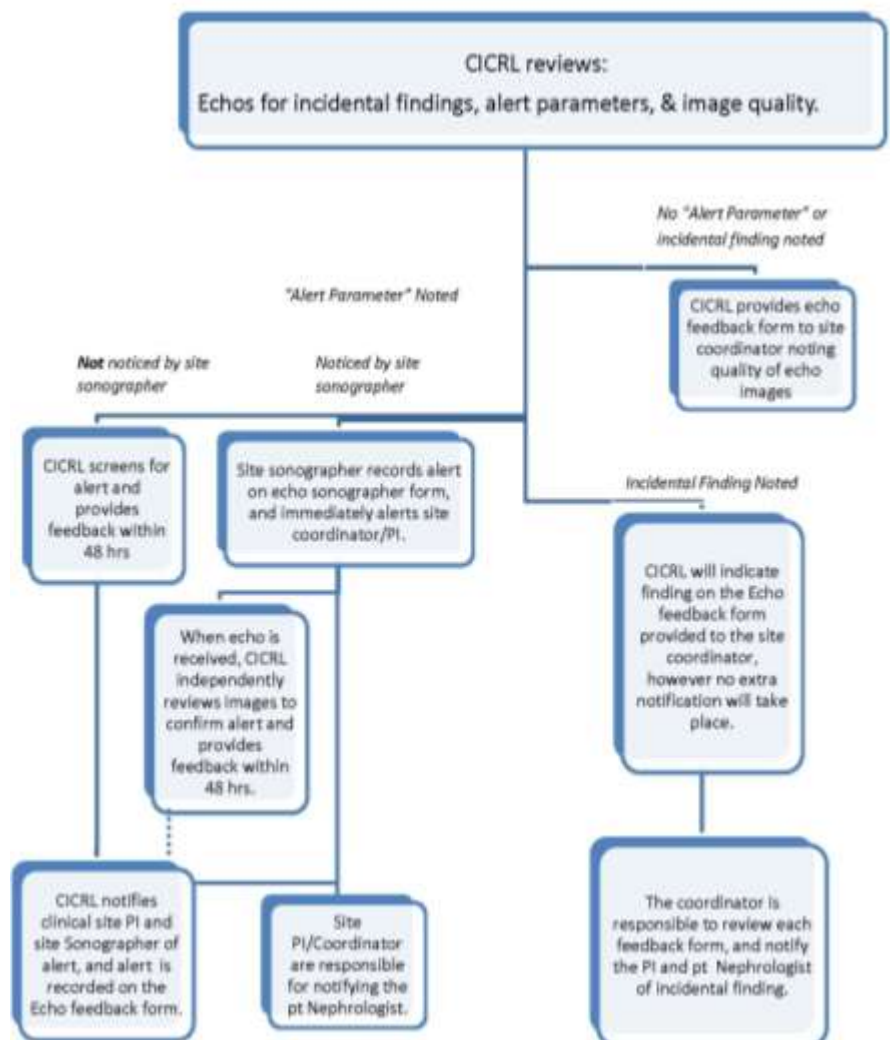


Local sites should screen for “Alert” findings. These echocardiographic conditions will trigger an “urgent” phone call from the sonographer or interpreting physician to the CKiD PI and study coordinator at the local site. The CKiD study coordinator and/or PI will then be responsible for calling the patient’s referring physician (or physician on record) on an “urgent” basis. The local sonographer will enter any of the “alert” findings listed, which they identify during the examination on the Echocardiographic Sonographer’s Worksheet.

Once the echo is received at the CICRL, the images are also screened for alerts. In the instance in which an “alert” parameter is picked up by the CICRL and has not been recorded on the Sonographer Worksheet (i.e., was not identified by the site sonographer), or was identified by the site sonographer, the CICRL cardiologist will review the echo to confirm the alert and the CICRL will provide feedback via email within 48 business hours to the PI and Clinical Site Sonographer. In the event that the site is interested in receiving more information, measurements for the parameters can be provided upon request.

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 via email by the CICRL. It is up to the site coordinator to then notify the PI and referring physician.

The flow sheet illustrates the CICRL review process.



19.8 SONOGRAPHER REVIEW AND CHECKLIST COMPLETION

Study Review

- **Scan study to assess for adequacy and completeness**
- **Total of 12 CKiD ECHO research images**
- **Complete Sonographer's checklist**
- **Complete CKiD Sonographer Self Critique Form**

19.9 FREQUENTLY ASKED QUESTIONS ABOUT CKiD ECHOS

Qualification Echos:

1. What's the turn around time for the "audition" echo to be reviewed by Cincinnati?
All studies will have an official response sent to the site from Cincinnati Children's Hospital Cardiovascular Core Imaging Laboratory within 48 business hours after receiving the study.
2. Is there a set standard by which the sample echo's to be reviewed, for example are they given a passing score?
The set standard is meeting the protocol requirements with no deficiencies. An approval/not approval status will be assigned by the Cincinnati Children's Hospital Cardiovascular Imaging Core Laboratory.
3. Is it possible for a site to have an audition tape not qualify? *Yes*
4. Who will provide the feedback if the images are not sufficient?
The Cincinnati Children's Hospital Cardiovascular Imaging Core Laboratory will provide feedback (See Qualification Flow Chart 19.2.1).
5. If there is a need for improvement, how long does a site have to submit another tape?
There is no set limit but it is to be done before actual study subjects are scanned for this project. A site needs to accomplish an "approval" status before study patients are scanned.
6. What if there is more than one echocardiographer at a site? Presumably the site will need to limit the number of echocardiographers to one or two?
The Cardiovascular Imaging Core Research Lab (CICRL) recommends that a primary sonographer is identified to perform all study patients. The primary sonographer will submit the qualifying echo to the CICRL & provide training to any additional sonographers

Study Echo's:

1. When the echo is performed, does the participating site/patient get a report or is the study for research purposes only? The families of the patients may be interested in knowing the results (for example: the neurocognitive tests will give some feedback to the families, and lab results from serum/urine studies are sent back to the sites)
Each individual field site (Echocardiography Laboratory) is responsible for disseminating "clinical" information on the patients they are scanning if they so choose. The Cincinnati Children's Hospital Cardiovascular Imaging Core Research Laboratory is responsible for the research component of the study, and will not assume clinical or diagnostic responsibility. For the purpose of research, studies in which cardiovascular findings are noted will be reported in the final analysis.
2. Is there a time limit by which the echo should be read by the central Cardiovascular Imaging Core Research Lab once it is received? *All studies will be read within 48 business days upon arrival to the Cincinnati Children's Cardiovascular Core Imaging Laboratory.*
3. How are the measurements being recorded? (For example is LV wall thickness measured x2 or x3?—for data quality)
All data are entered into an electronic record coded for confidentiality. All measurements will be measured three times for each of the structures or tracings of interest, with all three results reported as an average. All echocardiographic studies will be measured according to the American Society of Echocardiography guidelines and screened for "best beat".

4. Are there, “critical values” that should be sent back to the site. If there is, how are we going to handle this?
The Cincinnati Children’s Hospital Cardiovascular Core Imaging Laboratory will provide feedback via email on each study within 48 business hours after receiving the study.
5. If the echo for the study is incomplete or the sonographer cannot get a good acoustic window to allow for a good study, how should that be handled?
The sonographer should obtain the best quality images at all times, however it is realized that not all patients have adequate acoustic windows for measurement purposes. The sonographer is to fill out a CKiD Sonographer Self Critique Form in which they are to indicate comments regarding the study quality. If a study appears to have suboptimal or missing images, the Cincinnati Children’s Hospital Cardiovascular Imaging Core Laboratory will document this on the echo feedback form, and may contact the site coordinator and sonographer to discuss if a repeat study should be attempted

❖ *The Echo Feedback form on the next page will be sent to sites by the CICRL to provide feedback on the echocardiogram images. . The feedback is inclusive of incidental findings, “Alert Parameters” and image quality.*

19.10 ADDITIONAL QUESTIONS

All technical questions regarding echocardiographs not addressed under Section 19.9, Frequently Asked Questions should be addressed to the following:

Contact Information
Echo/CIMT Technical Questions

Core Lab Staff
Cardiovascular Imaging Core Lab Director
Michael Taylor, MD, PhD
Phone: (513) 803-0426
Email: Michael.Taylor1@cchmc.org

Cardiovascular Imaging Core Lab Sonographer
Lauren Longshore Brown, RDCS, RVT
Phone: (513) 803-5517
Email: Lauren.Longshore@cchmc.org

Echo Imaging Guidelines: Feedback Form

Adherence to the protocol

CKID Echo data:

Clinical Site #: _____

Correct Visit type #: _____

Incomplete Self Critique form: _____

Subject ID #: _____

Incomplete Sonographer Worksheet: _____

Date of Study: _____

Sonographer Initials: _____

Complete Echo submitted: _____

12 protocol images submitted: _____

Suboptimal images submitted: _____

Missing enough cardiac cycle loops to measure data: _____

Study ID on the acquired images (CD, video): _____

Sonographer Checklist

1. _____ Subject ID and site number entered correctly on tape/disk (no patient name is to be listed on tape/disk or worksheet)
2. _____ Complete Echocardiogram with M-Mode, 2D Doppler and Doppler of all valves. The Complete Echo is to be performed on the subjects first echo visit plus the 12 protocol images. Future echo visits on same subject only need the 12 echo protocol images acquired.
3. _____ Echocardiographic CKID Protocol study complete. (10 cardiac cycles per image, sweep speed 100mm/sec)
 - a) _____ Parasternal Long-Axis Image (**Image #1**)
 - b) _____ PLAX 2D-guided M-Mode of LV (**Image #2**)
 - c) _____ PLAX 2D-guided M-Mode of LA and Aorta (**Image #3**)
 - d) _____ 2D-parasternal short-axis image (papillary muscle level) (**Image #4**)
 - e) _____ 2D Apical 4-chamber image (**Image #5**)
 - f) _____ 2D Apical 2-chamber image (**Image #6**)
 - g) _____ Mitral Inflow Pulse Wave Doppler (**Image #7**)
 - h) _____ Pulse Wave Tissue Doppler Imaging
 - 1) _____ Medial mitral annulus (**Image #8**)
 - 2) _____ Lateral mitral annulus (**Image #9**)
 - i) _____ Suprasternal notch (high parasternal) short axis image of the aorta (**Image #10**)
 - j) _____ Suprasternal notch (high parasternal) short axis of the aorta ZOOMED (**Image #11**)
 - k) _____ Suprasternal notch (high parasternal) short axis of the aorta- 2D guided M-Mode of ZOOMED image (**Image #12**)
4. _____ “Alert” protocol followed (if applicable). “Alert” Finding (specify): _____
5. _____ Videotape/disk copied and stored. Both tapes/disks labeled with clinical site, patient ID and study date.

Comments: _____

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY
SECTION 20: ECHO DATA TRANSMISSION AND SUBMISSION

20.1 DATA TRANSMISSION

DATA Transmission

- Each study will be recorded on videotape/CD – 1 study per tape/CD
- Copy tape prior to shipping & store copy in secure place
- **Original study sent FedEx to:**
Cincinnati Children's Cardiovascular Core Research Lab
Cardiology Dept., ML 2003
Attn: Lauren Longshore Brown
3333 Burnet Ave.
Cincinnati, OH 45229
513-803-5517
- **FedEx slip:**
 - Contact your CCC for a FedEx slip (if needed) and it will be emailed to you.

DATA Transmission

- Each tape/CD should be labeled with the study name (CKID), clinical site, patient ID number & date of study.
- Copy Sonographer Checklist & Self Critique Form, place one copy in patient record at local site & include second copy in shipment with corresponding study tape/CD

20.2 ECHO CORE LAB DATA ENTRY

20.2.1 Database Entry of Imaging Media I.D. Numbers

- In the Cardiovascular Imaging Core Research Lab (CICRL), information from the field center Echocardiographic Sonographer Worksheet containing participant's I.D. (KID ID) is entered by the CICRL sonographer into a specially configured database maintained on both hard-disk of dedicated PC and on-line server (as a back-up).
- Linkage of this database with that at the Data Coordinating Center via I.D. numbers will facilitate use should partial re-reads be required for quality assurance. Data entry will include study name, VHS tape number, clinical site identification, participant's I.D. (KID ID) and echo acquisition date and the date when echo is received by CICRL.
- The participant's ID (KID ID) and site numbers will be distributed by the Data Coordinating Center at Johns Hopkins and it will be verified using the digit verification program, so incorrect I.D. entries can be identified and corrected.

20.2.2 Echocardiographic Core Lab Reading Procedure

- Measurements will be made by assigned CICRL sonographers (cardiovascular specialists with expertise in Pediatric Echocardiography; they will have assigned ERL Sonographer I.D.) using a computerized review station. Imaging media will be scanned by CICRL sonographers to identify appropriate segments of 2-D and 2-D guided M-Mode recordings of LV, Aortic root, Left atrium, mitral inflow, PW Doppler and mitral annulus myocardial tissue imaging for digitization (for VHS tapes/disks), measurements, calculations and storage. Three beats of each parameter will be measured and averaged.

The completed VHS tapes/disks will be stored, in numerical order, in special locked cabinets in the reading laboratory.

20.3 DATA FORMAT AND DELIVERY

Data will be delivered to the DCC (KIDMAC) in ASCII and excel files. Data will be compiled into the desired format. However, it should be noted that many other formats may be used. Three (3) measurements for each variable will be included in the file. The file or group of files will be transmitted to DCC on monthly basis using a secure file sharing service.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 21: CAROTID ULTRASOUND EXAMINATION FOR SUBCOHORT

21.1 OVERVIEW

Ultrasonographic measurements of carotid artery intima-media thickness (IMT) have proven to be predictive of subsequent cardiovascular and cerebrovascular events. In a subgroup of children enrolled in CKiD, carotid IMT will be determined by ultrasonographic measure. The sub-cohort of patients will be identified from the centers that are able to perform high frequency carotid artery ultrasound. Up to 7 clinical sites have been chosen to participate in the carotid IMT studies.

21.2 STUDY PREPARATION

Study Preparation

- **Carotid ultrasound** will be performed at visit 2, 6, 10, and 14.
- **Explain procedure:** Purpose of procedure will be explained. Stress that it is painless.
- **Position the subject:** The patient will be asked to lie supine on the echo table. The head is slightly extended and turned contralaterally to the carotid artery being examined.

21.3 MACHINE PREPARATION

Machine Preparation

- **Prepare Transducer:** Check to see that linear array transducer is loaded into the appropriate slot (below main panel) and switch is turned to lock position.
- **Activate Vascular Preset**
- **Apply liberal amount of gel to transducer**

21.4 SEQUENCE FOR CAROTID ARTERY

Sequence for Carotid Artery Evaluation-Patient Preparation

- **Subject in supine position on exam table with ECG leads appropriately placed**
- **Subject should be lying with head at the top of the exam table with slight hyperextension of the neck**
- **Turn head approximately 45 degrees to the left**

Carotid Artery Anatomy: The Carotid Artery Is Divided Into Three Segments:

Distal Common Carotid Artery (CCA): the distal 1.0 cm of the straight part of the artery immediately proximal to the beginning of the bifurcation. The key anatomical feature that defines this segment is the crest or lip at the beginning of the dilation.

Carotid Bifurcation or Bulb (**CB**): Two anatomical references allow the identification of the CB:

- The inferior extent of the CB is the crest at the origin of bifurcation
- The superior extent of the CB is the highest point in the arch of the flow divider separating the origin of the internal and external carotid arteries.
(Length varies among subjects).

Proximal Internal Carotid Artery (**ICA**): the proximal 1.0 cm of the ICA beginning at the flow divider crest

21.5 CKiD CAROTID ARTERY PROTOCOL

CKiD Carotid Artery Protocol

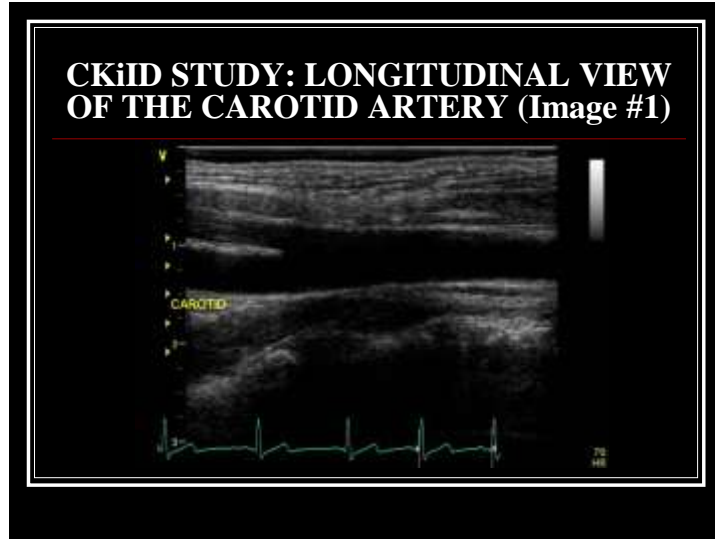
- All B-mode ultrasound imaging will be obtained using high resolution linear array 5.0-12.0 MHz vascular ultrasound transducer.
- The images are to be recorded on Super VHS tape /CD
- The carotid artery will be imaged in the longitudinal view and cross-sectional views within the distal common carotid artery, bulb and the proximal internal carotid artery.
- Images will include the vessel adventia, media and intima. The goal is to examine the associations of arterial thickness and stiffness with LV structure, and systolic and diastolic function.

21.6 QUALITATIVE B-MODE SCANNING

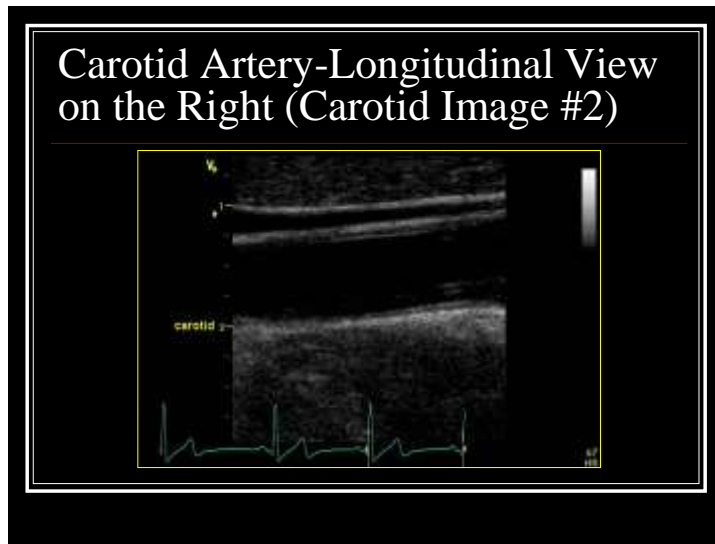
Qualitative B-Mode Scanning (3 Segment Identification and Plaque Detection)

- Begin on the **RIGHT** & annotate "**RIGHT**" on the screen
- Scan the entire carotid artery: locate the 3 anatomic segments.
- Magnify the image using the "pan/expand" setting on the ultrasound instrument to enlarge the image to the maximal size possible while maintaining all pertinent structures on the screen.
- Continuous scanning will be performed in the anteroposterior and coronal planes from the lower to the higher third of the right and left carotid arteries.

21.7 LONGITUDINAL VIEW OF THE CAROTID ARTERY



The sonographer should identify the carotid bifurcation with the focus zone at the level of interest. The sonographer should image the carotid artery in both longitudinal and cross-sectional views and images should include the vessel adventitia, media and intima of the far wall.



Place the transducer on the skin such that a longitudinal image of the midportion of the right common carotid artery (**RCCA**) is seen. Use very light pressure on the transducer. Move the transducer cranially and rotate anteriorly and posteriorly until the crest of the bifurcation is seen. Adjust the gain and time gain settings to optimize visualization of the 6 interfaces required for measurement of arterial wall thickness. Use the lowest settings possible to reduce artifact. Keep the transducer perpendicular to the vessel and scan back and forth until the best image of near and far wall lumen/intima-media and intimal-media/peri-adventitial interfaces are visualized. Concentrate on obtaining the far wall image as this is the most important wall that will be measured. Record while scanning superiorly/inferiorly and left/right to locate the thickest interface. When an area of thick interface is located, record a few seconds in that location before continuing the sweep.

Repeat on Left side of the neck

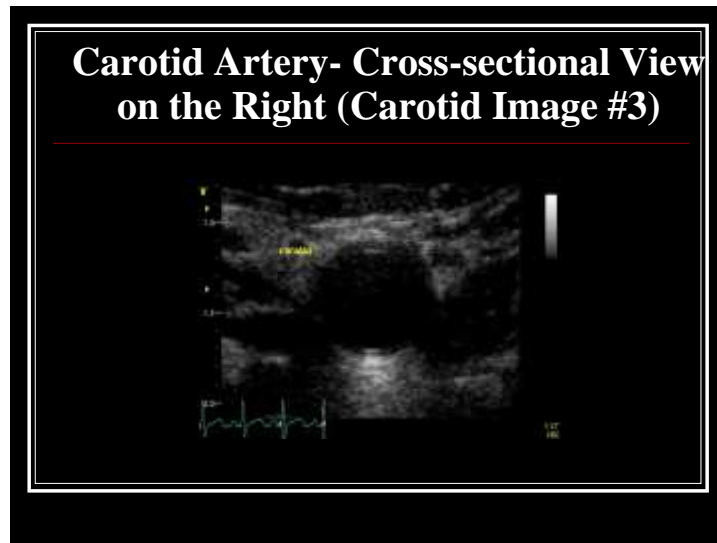
At least 10 cardiac cycles should be obtained.

21.8 CAROTID INTIMAL MEDIA THICKNESS MEASUREMENT

Carotid Intimal Media Thickness (c-IMT) Measurements

- **Obtain peak systolic and end diastolic diameter for 10 cardiac cycles from longitudinal view**
- **Obtain peak systolic and end diastolic diameter for 10 cardiac cycles from cross-sectional views**

21.9 CAROTID ARTERY – CROSS-SECTIONAL VIEW



- Obtain end systolic and diastolic diameter for 10 cardiac cycles from cross-sectional views

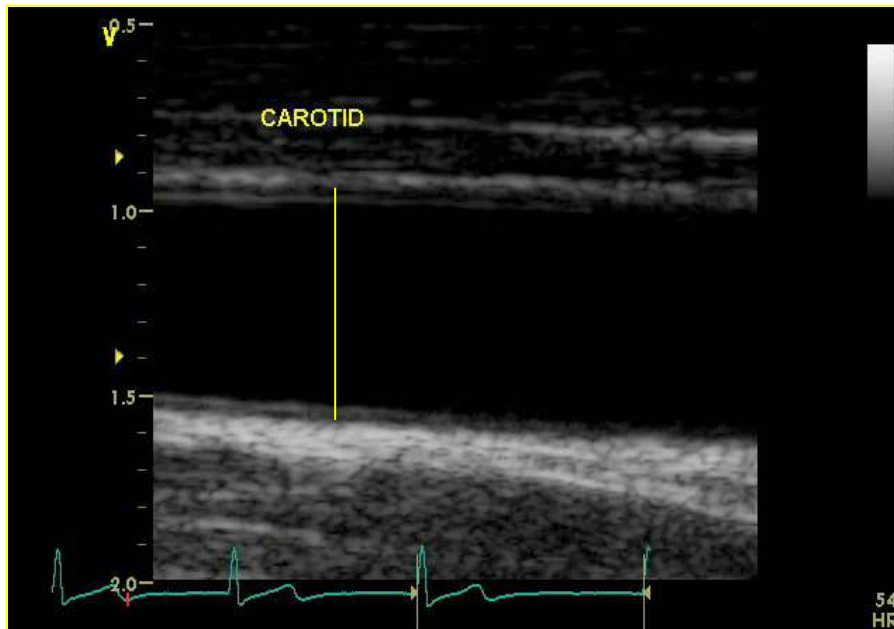
Orient the probe in the transverse position at the origin of the common carotid artery (near clavicle) just proximal to the bifurcation. Images should include the vessel adventitia, media and intima.

Repeat Carotid Scan on the Left

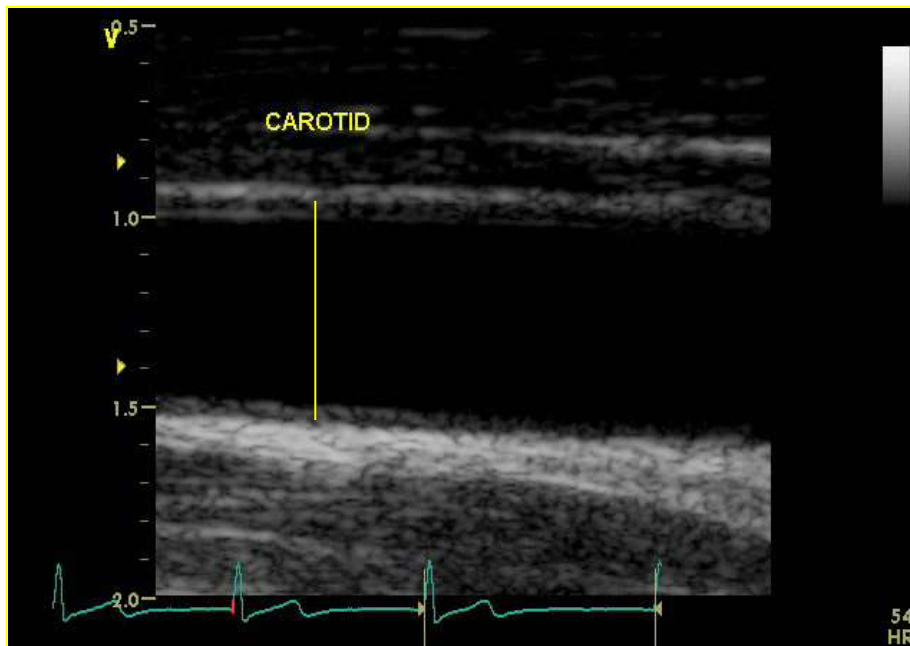
- Annotate **"LEFT"** on the screen
- Carotid Image #4- Longitudinal Bifurcation of the Left Carotid Artery
- Carotid Image #5 - Artery-Longitudinal View on the Left
- Carotid Image #6 - Cross-sectional View on the Left
- **Obtain 10 cardiac cycles of Image #4, 5, & 6.**

21.10 ECHO CORE LAB CAROTID ARTERY MEASUREMENTS

Carotid Artery Measurements

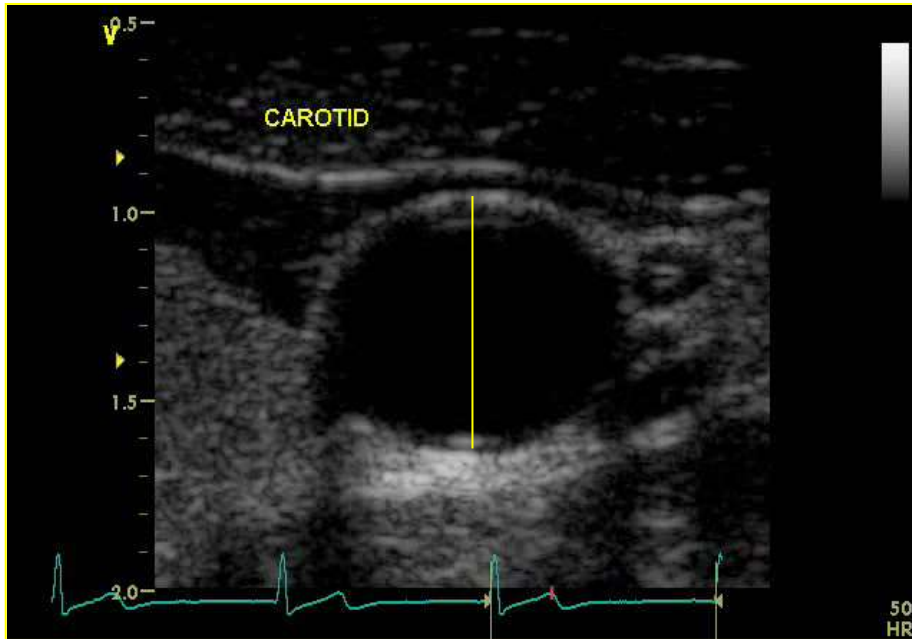


Longitudinal view of the carotid artery at end-systole

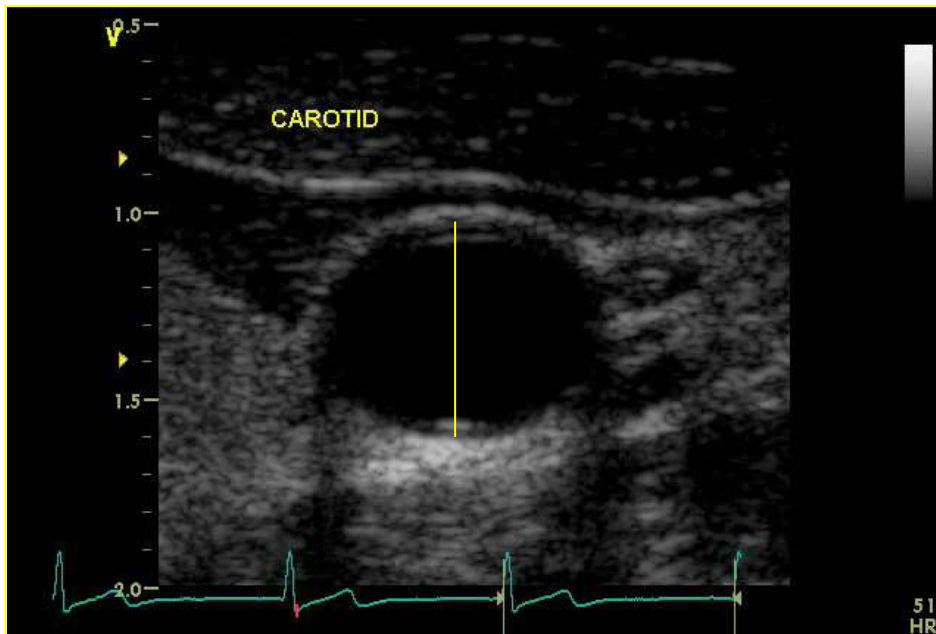


Longitudinal view of the carotid artery at end-diastole

Carotid Artery Measurements

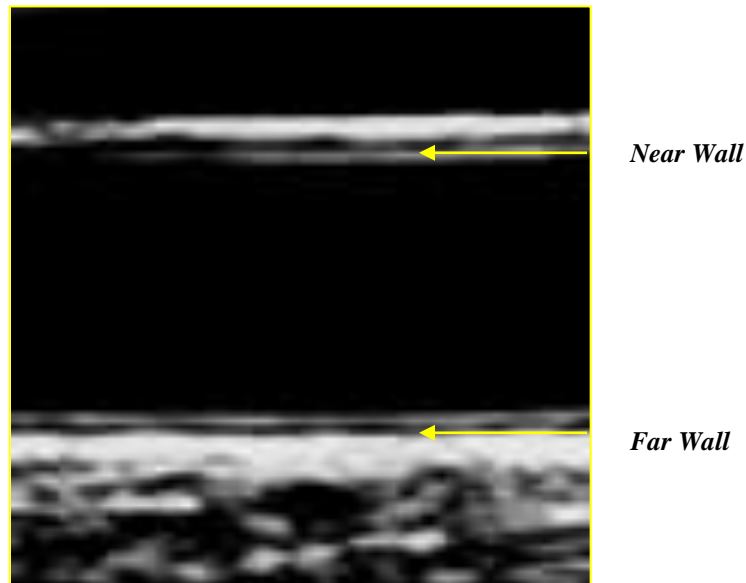


Cross-sectional view of the carotid artery at end-systole

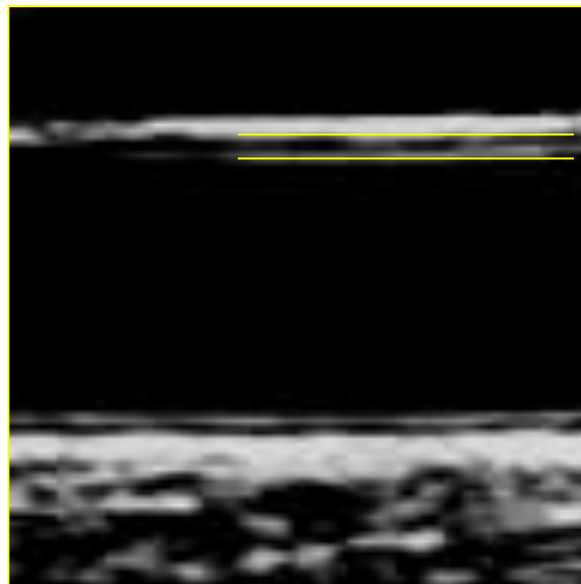


Cross-sectional view of the carotid artery at end-diastole

Measurements of the near and far wall will be done offline of the intimal thickness by making a mark from the leading edge of the intima to the media adventitia interface (the trailing edge of the adventitia)



Anterior (near) and posterior (far) walls of the carotid artery are displayed as two bright white lines separated by a hypoechoogenic space



Best estimate of the near-wall intima-media thickness - distance between the trailing edge of the first bright line and the trailing edge of the second bright line

Carotid artery compliance calculations:

Distensibility

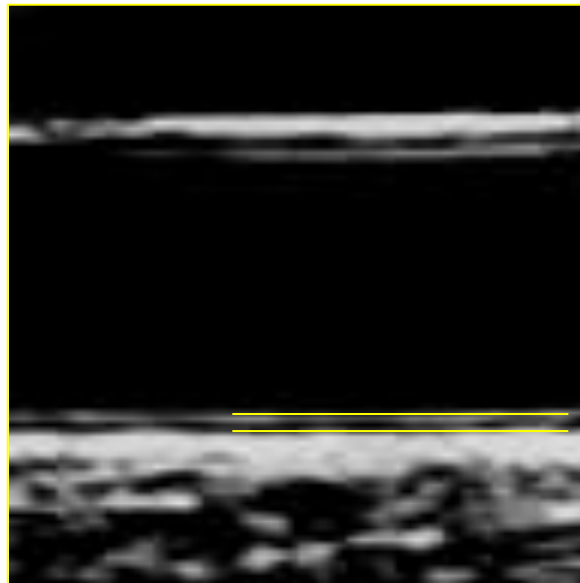
$$DC = 2(\Delta D/D)/(SBP-DBP)$$

D-carotid artery diastolic diameter and ΔD -change in artery diameter during systole.

Stiffness parameter

$$\beta = (\ln[SBP/DBP])/(\Delta D/D).$$

Carotid Artery Measurements



Distance between the leading edge of the first bright line of the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness

21.11 SONOGRAPHER VASCULAR WORKSHEET AND SELF-CRITIQUE

21.11.1 CKiD carotid IMT Worksheet

Clinical Site #: _____

Subject ID #: _____

Sonographer Initials: _____

Date of Study: _____

Regular Study Visit:

- V2
- V6
- V10
- V14

- Irregular (Accelerated) Visit ____

Post RRT Study Visits:

- DV1b TV2
- DV2 TV4
- DV3
- DV4
- DV5

- Irregular (Accelerated) Visit ____

Is this a Repeat carotid IMT?

- Yes No

Sonographer Checklist

Check When carotid IMT Study Completed

1. _____ All of the above worksheet data filled in.
2. _____ Subject ID and site number entered correctly on tape/disc (no patient name is to be listed on tape or worksheet)
3. _____ Completed CKiD vascular study including the following images:
 - a) _____ Cross-sectional right carotid artery view (10 cardiac cycles) (**Carotid Image #3**)
 - b) _____ Longitudinal bifurcation right carotid artery view (10 cardiac cycles) (**Carotid Image #1**)
 - c) _____ Longitudinal right carotid artery view optimizing the distal 2 cm of CCA for IMT measures (10 cardiac cycles) (**Carotid Image #2**)
 - d) _____ Cross-sectional left carotid artery view (10 cardiac cycles) (**Carotid Image #6**)
 - e) _____ Longitudinal bifurcation left carotid artery view (10 cardiac cycles) (**Carotid Image #4**)
 - f) _____ Longitudinal left carotid artery view (10 cardiac cycles) (**Carotid Image #5**)
4. _____ Videotape/disc copied and stored. Both tapes/discs labeled with clinical site, patient ID and study date.

Shipment Directions for CKiD Sonographer:

- Make a copy of this form. Keep a copy for CKiD records. Mail original form with the carotid IMT Self Critique Form and Videotape/CD to:

CCHMC
Attn: Lauren Longshore
Cardiology Dept., ML 2003
3333 Burnet Ave.
Cincinnati, OH 45229
513-803-5517
Lauren.Longshore@cchmc.org

FedEx Slip:

- Contact your CCC for a FedEx slip (if needed) and it will be emailed to you

CKiD carotid IMT Self Critique Form

Clinical Site ID #: _____ Sonographer Initials: _____ Is this the Primary Sonographer Y N

Subject ID #: _____ CKiD exam date: _____

Regular Study Visit:

- V2
- V6
- V10
- V14

Post RRT Study Visits:

- DV1b TV2
- DV2 TV4
- DV3
- DV4
- DV5

Is this a Repeat carotid IMT? Yes No

Irregular (Accelerated) Visit _____ Irregular (Accelerated) Visit _____

Directions: The CKiD Sonographer will fill out the information below.

Circle YES or NO

1. Is the subject ID displayed correctly on the image?
2. Did the Sonographer fill out cIMT Worksheet?
3. Were a minimum of 6 required images recorded?
4. Was overall gain set appropriately?
5. Was the TGC set appropriately?
6. Was the depth set appropriately?

- Yes No
- Yes No
- Yes No
- Yes No
- Yes No
- Yes No

Comments:

Directions for CKiD Sonographer:

- Make a copy of this form. Keep a copy for your records. Mail original form with the carotid IMT Worksheet and Videotape/CD to:
CCHMC
Attn: Lauren Longshore
Cardiology Dept., ML 2003
3333 Burnet Ave.
Cincinnati, OH 45229
513-803-5517
Lauren.Longshore@cchmc.org

FedEx slip:

- **Contact your CCC for a FedEx slip (if needed) and it will be emailed to you**

21.12 QUALITY CONTROL PROCEDURES FOR CAROTID ARTERY AND CARDIAC ULTRASOUND

Quality control procedures will be implemented during all stages of data collection to calculate objective measurements of variability to assess reproducibility. The same quality control procedures are used for both carotid artery and cardiac ultrasound. These quality assurance procedures are designed to determine biologic, technical and operator variability across the entire data collection and processing procedure.

21.12.1 Training at the Cardiovascular Core Imaging Lab

Re-training in all aspects of the protocol will occur yearly along with discussion of QC results. Core Lab sonographers will be supervised by Dr. Michael Taylor director of the Core Imaging Lab.

- Cardiovascular Imaging: Training of sonographers in cardiac ultrasound and data acquisition will be performed by Dr. Michael Taylor director of the Core Imaging Lab.

21.12.2 Scanning Variability

A. Image Acquisition.

1. Echocardiography: Quality of the echocardiograms received will be assessed using the criteria of Schieken et al. These criteria require the presence of a single dominant line on the area of the M-mode tracing to be measured, continuity of the line for 5mm in length, and an interface with motion characteristics for the specific cardiac structure being imaged.
 2. Carotid Ultrasound: Carotid artery images will be excluded from the study if the arteries are extremely tortuous or did not have identifiable reference markers or have lesions that can not be measured due to acoustical shadowing according to published guidelines. (Ferrara) Other specific criteria for a high-level ultrasound are presence of adventitia-media interface and intima-lumen interface in at least two arterial segments.
- B. Blind Duplicate scans: A random sample of 10% of all subjects will undergo a repeat carotid and cardiac ultrasound examination. The repeat studies will be labeled with the blind duplicate identification number each participant was assigned upon entry into the study. A fictitious name is assigned to ensure complete blinding of the readers.

21.12.3 Sonographer Analysis Variability

- A. Analysis technique: All measurements will be performed three times for each of the structures or tracings of interest, with all three results reported as an average.
1. Echocardiography: All echocardiographic studies will be measured according to American Society for Echocardiography guidelines and screened for “best beat”.
 2. Carotid ultrasound: Studies will be read from leading edge to leading edge according to accepted conventions (ARIC protocol).
- B. Blind Duplicate Analyses: A different random sample of 10% of all original (not blind duplicate) carotid and cardiac studies will be re-analyzed in a blind fashion.

21.12.4 Statistical Analysis

- A. Data will be entered into an electronic record coded for confidentiality.
- B. Data sets will be edited electronically with manual review of original source documents for outliers.
- C. Inter-sonographer and intra-sonographer coefficients of variation and Intra-class correlation coefficients will be calculated for each measure of cardiac and carotid structure and function for both the scanning and reader variability studies. These will be performed periodically (every 6 months) to ensure adequate reproducibility.

21.13 QUESTIONS AND FEEDBACK TO SITES

Refer to Section 19.7 for information regarding “Alert” parameters and incidental finding and Section 19.9 for Frequently Asked Questions about echos, which would be similar for cIMT.

All other technical questions regarding echocardiographs and carotid ultrasounds should be addressed to the following:

Contact Information

Echo/CIMT Technical Questions

Core Lab Staff

Cardiovascular Imaging Core Lab Director

Michael Taylor, MD, PhD

Phone: (513) 803-0426

Email: Michael.Taylor1@cchmc.org

Cardiovascular Imaging Core Lab Sonographer

Lauren Longshore Brown, RDCS, RVT

Phone: (513) 803-5517

Email: Lauren.Longshore@cchmc.org

❖ *The form below will be sent to sites by the CICRL to provide feedback on the carotid ultrasound images.*

CIMT Imaging Guidelines: Feedback Form

Adherence to the protocol



Review of Submitted CKiD CIMT study:

- Clinical Site #: _____
- Correct Visit #: _____
- Complete Self Critique form: _____
- Subject ID #: _____
- Complete Sonographer Worksheet: _____
- Date of Study: _____
- Sonographer Initials: _____
- Minimum of 6 CIMT protocol images submitted: _____
- Suboptimal images submitted: _____
- Enough cardiac cycle loops to measure data: _____
- Study ID and Correct annotation on all acquired images (CD, video): _____

Sonographer Checklist

- 1. _____ Subject ID and site number and sonographers initials entered correctly on tape/disk (no patient name is to be listed on tape/disk or worksheet)
- 2. _____ Acquired 6 CIMT protocol images.
- 3. _____ CIMT CKiD Protocol study complete. (10 cardiac cycles per image, sweep speed 100mm/sec)

Right Side

- 1) _____ Longitudinal Bifurcation of the Right Carotid Artery (Carotid Image #1)
- 2) _____ Carotid Artery-Longitudinal View on the Right (Carotid Image #2)
- 3) _____ Carotid Artery- Cross-sectional View on the Right (Carotid Image #3)

Left Side

- 4) _____ Longitudinal Bifurcation of the Right Carotid Artery (Carotid Image #4)
- 5) _____ Carotid Artery-Longitudinal View on the Right (Carotid Image #5)
- 6) _____ Carotid Artery- Cross-sectional View on the Right (Carotid Image #6)

- 4. _____ “Alert” protocol followed (if applicable). “Alert” Finding (specify): _____
- 5. _____ Videotape/disk copied and stored. Both tapes/disks labeled with clinical site, patient ID and study date.

Comments:

PLEASE NOTE: *Sherry Turner no longer is the CICRL contact for CKiD. All images and correspondence should be directed to Vicky Moore.*

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 22: PUBLICATION POLICY AND ANCILLARY STUDIES

22.1 BACKGROUND AND PURPOSE

The Chronic Kidney Disease in Children Cohort Study (CKiD) will use a multi-site, prospective study design 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. When deemed appropriate and beneficial, the CKiD Steering Committee (SC) also intends to combine CKiD data with other homologous cohort data to address research questions common to both studies. The CKiD SC, consisting of the principal investigators from each CKiD clinical coordinating centers, the National Institutes of Health (NIH), the CKiD Data Management and Coordinating Center (KIDMAC), the CKiD Central Biochemistry Laboratory (CBL) and Principal Investigators from some clinical sites, intend that key findings from this multicenter study be presented and published widely, promptly, and be of the highest quality.

The purpose of this publication policy is to ensure that these important multicenter research findings from the Chronic Kidney Disease in Children Cohort Study be developed collaboratively, efficiently and fairly among the collaborators from each of the participating sites, the NIH and KIDMAC. Additionally, it is the purpose of this policy to ensure an efficient, fair and coordinated collaboration with other outside investigators or other cohort studies on all research questions deemed appropriate for joint analysis.

22.2 DEFINITIONS

The publication policy is designed to address all investigations which may use data collected in this study. The basis for determination of these definitions will over time fall to the SC voting members, a subcommittee of the Steering Committee.

The CKiD SC recognizes two categories of investigators and two categories of investigations:

1. **CKiD INVESTIGATORS (CKiD-I)**
CKiD-I 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.
2. **CKiD EXTERNAL INVESTIGATORS (CKiD-E)**
CKiD-E are defined as any investigator who does not meet the criteria to be a CKiD-I. In addition, CKiD-I who cease to meet the definition of CKiD-I will be 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 22.3.4 below.
3. **CORE INVESTIGATIONS**
Core investigations are those designed to accomplish the study objectives that are common to all CKiD sites. Analyses and publications or presentations resulting from this data will be developed by a writing committee formed by the CKiD collaborators and confirmed by the Steering Committee. As shared data, these investigations and publications will have priority over secondary or ancillary investigations.

4. SECONDARY/ANCILLARY INVESTIGATIONS

Secondary investigations are those that rely upon data collected as part of this study but which are unrelated to study-wide hypotheses. CKiD investigators may propose such investigations on their or their consortium's behalf.

22.3 PROCESS FOR CORE CKID PROPOSALS

22.3.1 Development of Proposals for Analyses of Core CKiD Study Questions

The CKiD SC is responsible for overseeing specific written and oral communications concerning core hypotheses/research questions described in the CKiD research models for publication and presentation at scientific meetings. To facilitate this process, initial discussion and prioritization of publications or presentations based on the primary research questions will be generated by the CKiD Scientific Area-Based (SAB) Subcommittees with final review by the CKiD SC.

Submissions dealing with the CORE hypotheses will have priority over ancillary submissions, both in terms of timing and in use of study resources for data analysis. Analyses of hypotheses related to the CKiD research models shall not be published or presented using individual site data prior to the submission for publication of studies of these hypotheses using pooled (study-wide) data unless approved by the SC.

22.3.2 Submission of Proposals

Requests to use data collected by CKiD must be completed using the CKiD study proposal form or “concept sheet” available online at www.statepi.jhsph.edu/ckid. Completed concept sheets should be emailed to KIDMAC to the attention of Judith Jerry-Fluker (jjerry@jhu.edu) for posting and SC review. The proposal should be brief (2-3 pages), using the latest version of the submission form:

- a. proposed title, and names of possible investigators
- b. background information, rationale for the analyses
- c. specific aims, hypotheses to be tested
- d. study design (i.e., type of study) and methods
- e. specific inclusion and exclusion criteria
- f. laboratory methods
- g. quality assurance/quality control procedures
- h. statistical approaches to be used and rationale for analyses: this should include power calculations relevant to the proposed study question
- i. identification of variables and description of their role: dependent, independent, effect modifier, etc.
- j. numbers, types and volume of specimens needed, if applicable
- k. timetable for completion of project, including deadlines for submission of abstract, data analyses, and first draft of paper

Investigators are encouraged to develop studies in conjunction with one or more of the scientific subcommittee members listed in Section 2. Study proposals dealing with CKiD specific aims outlined in Section 1 of the Manual of Procedures 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, sites, central laboratories, and KIDMAC.

Ethical consideration of human subjects includes 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 delivered to KIDMAC.

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) inclusion of at least one CKiD participant enrolled in the main study.

22.3.3 Review and Approval of Proposals

The primary investigator will submit his/her concept sheet to KIDMAC via e-mail using the most current version of the Concept Sheet Proposal Form. Concept sheets submitted on the wrong form will be returned with a request for resubmission on the correct form.

If overlapping proposals are submitted to the SC, it is the SC's responsibility to suggest how they may be combined and re-submitted as one proposal potentially involving investigators from more than one research area or how they may be revised and re-submitted as two separate, non-overlapping proposals, or to choose the proposal with the greatest overall merit.

Once submitted to KIDMAC, KIDMAC will post the concept sheet (CS) to the "Submitted Concept Sheets" bulletin board on the CKiD private web site. The posting will include the title and the lead author of the proposal and the target date for review by the full SC. KIDMAC will also e-mail the SC members when this information has been posted to the web site. 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 the semi monthly conference call, inviting the Primary Investigator and Primary Reviewer. This process will occur in a timely manner, attempting to provide feedback to the primary investigator within 4 weeks of submission. The SC will assess the CS using various criteria: whether the work is duplicative, whether the CS reflects high quality science, whether the CS presents a significant use of resources, whether data is available, and whether the concept represents "hot" science and might be eligible for fast-tracked journal submission. The SC can also suggest corrections and revisions. Comments on a particular proposal may be posted as a reply on the bulletin board. The SC will include all comments in their decision. The SC will inform the primary investigator of the status as: approved, rejected or deferred (revisions requested).

The primary investigator will be emailed the final decision and project number (see below), referencing any SC changes to the CS, and request their response to any comments via posting. The author of the proposal will have approximately one week to address any concerns that may have been voiced on the discussion board. Significant changes in a concept or in the variables to be analyzed will require resubmission of the proposal as outlined above in Section 22.3.2.

Removal of CKiD specimens from the NIDDK repository for analysis requires prior approval by the SC,

and prior authorization by both KIDMAC and the Repository Project Officers before KIDMAC will request samples. The process for requesting CKiD repository samples is outlined in Section 30 of the Manual of Procedures.

If approved, KIDMAC will assign the concept sheet a study number in the form of k-YY-###, where “k” 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 KIDMAC 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 KIDMAC and obtaining a fully executed data use agreement. 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.

22.3.4 Formation of Writing Committee

After a CS is approved, requests will be sent out for co-author and senior co-author (MNJ) assignment to principal investigators. Principal investigators carefully select their sites’ representative on the paper. Failure to name an author, who must be willing to be an active participant, within 2 weeks will result in the site having no author. MNJ authors should be in communication with the lead author and receive all data sets and manuscript versions.

The number and composition of the people in a writing committee 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 coordinating center of the primary investigator whom also must be named on the concept sheet; (b) up to two investigators from each of the other two centers; 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 center. 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 coordinating centers of the study; and (c) up to two members from NIH or other major collaborating centers. 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 coordinating centers of the study. Ancillary or secondary studies do not need to have a co-author from each of the three coordinating centers of the study. In accordance with the responsibility of co-authorship in scientific publications, individuals should only be co-authors 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 co-author. Such right is appropriate, for example, not to include authors in specialized methodological papers when there are no individuals with expertise at a particular center (e.g., a new genetics method).

The lead author is responsible for the completion of the manuscript, as well as the determination of authorship order. The lead author of the writing committee will be responsible for requesting and facilitating a conference call early in the planning of the analysis. Writing assignments should be given to those interested committee members at this time. A proposed order of authorship should also be considered at the time writing assignments are distributed.

Specific tasks of the lead author include:

- a. Determining authorship order.
- b. Obtaining consensus on the authorship order from the writing committee.
- c. Notifying KIDMAC within one month of appointment of:
 - i. the list and proposed order of the writing committee membership;
 - ii. proposed analysis target dates for abstract and first draft of paper; and
 - iii. proposed target date for paper submission.(The above timeline should follow the standards set in Section 22.3.5)
- e. Coordinating with KIDMAC to ensure that data analyses are distributed to writing committee members in a timely fashion.
- f. Notifying the SC (or designated committee) of significant problems or delays in completion of analyses or writing of drafts, or the need for changes in authorship.
- g. Notifying the writing group of manuscript submission to the SC.
- h. Notifying KIDMAC and the SC chair's assistant of outcomes of journal submission.

22.3.5 Timelines for Manuscript Development

At the time of writing committee assembly a biostatistician will be assigned to the project. That individual will contact the investigator within a week of assignment to discuss the optimal format for analytic data set requests. The analytic request should then follow within 2 weeks. As a proposed subsequent time-line: Assembly of analytical data set should follow 0.5 to 1 month after receipt of request. Preliminary statistics, data visualization, descriptions, exploration should be complete 1 to 2 months after CS prioritization. A focused statistical analysis aimed at addressing research questions including draft of figures and tables to be included in the paper would follow within a month.

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. If a writing committee member does not actively participate in the writing and/or review process, then he/she may be removed from the writing committee. Also, 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.

22.3.6 Data Specimens and Analysis Requests

Once a project is approved, the lead author should communicate with KIDMAC to start collaboration in study design, creation of analytical datasets, selection of repository specimens, and data analysis.

Data requests should be submitted to KIDMAC as a list including each CKiD variable name for which data are needed, the form number(s) on which the variables are located, and the visit number(s) and/or calendar dates for which data are needed. Variable names can be obtained from the private CKiD Data Management System website. A KIDMAC repository coordinator (KRC) will be assigned to the project once a data request has been made. If a request for data analysis is made but it is not to be done by KIDMAC, then KIDMAC will normally require two weeks for the production of an analytic database. Longer time may be required for complex data requests.

Once the list of specimens has been generated, a request for obtaining the specimens is forwarded to the NIH Repository Officer for sign-off. Once approval is obtained, KIDMAC will contact the repository to

arrange shipment of the specimens.

NOTE: Requests for specimens will not be processed until verification of local IRB approval has been provided.

It is anticipated that, during the analysis phase, KIDMAC team members will primarily and intensively communicate with the writing group chair (and perhaps a few others). The writing chair is responsible for updating working groups and other members of the writing committee.

Once abstracts and manuscripts are written and finalized among members of the writing committee, they should be sent to the SC for review and approval.

22.3.7 Review of Abstracts, Presentations

Final abstracts and presentations must be reviewed and approved by a SC voting member before any presentation at a formal scientific meeting or prior to submission for publication. These requests will be expedited by KIDMAC based on deadline dates and must meet SC and NIH guidelines.

Abstracts will be submitted electronically to KIDMAC and should include information on the intended meeting, due date for the abstract, and type of study (core, site-specific, etc.). Abstracts will be posted on the CKiD private website and PIs will have one week to comment on the abstract and recommend acceptance, rejection or acceptance with revisions. The investigator will receive all comments and have the opportunity to make changes. The site PI will have the responsibility to review the final abstract to be sure it incorporates critical comments. Investigators will be encouraged to follow the above procedure. Last minute abstracts should be few and the responsibility for review and recommendation will fall to the site PI who will report to the SC on the subsequent scientific call.

22.3.8 Review of Manuscripts by Steering Committee

Once the manuscript has been approved by the co-authors, it should be submitted electronically to KIDMAC prior to submission to journals. Manuscripts will be posted to the "Manuscripts" bulletin board. The posting will include the title and lead author of the proposal. 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. If appropriate, at the same time a Scientific Area-Based Subcommittee chair will assign an expert in the field to review the manuscript.

Manuscripts are processed in much the same manner as CS. The primary reviewer (PR) will review the manuscript and use co-author and SC members' comments to decide the outcome of the manuscript. Co-authors are required to post their approval/disapproval of the manuscript version. Anyone with comments on a particular manuscript may post them as a reply on the web site.

KIDMAC will e-mail SC members indicating when a manuscript is posted to the web site and when it will be due for review on the full SC call.

If a co-author disagrees with a manuscript or finds the manuscript to be misleading about CKiD data they need to first attempt to resolve the issue with the writing group/co-authors before submitting to the SC. If a co-author still finds fault with the version submitted to the SC, they should indicate that on the discussion board. The PR will review the comments and the full SC can eventually be asked to review the manuscript and discuss any concerns.

Lead authors are responsible for informing KIDMAC regarding the outcome of any journal submissions. If a manuscript is accepted for publication, lead authors must also send a Portable Document Format (.pdf) version of the published article.

Presentations or manuscript submissions which do not have prior SC approval and NIH notification are inconsistent with the spirit of collaborative research. Disregard of this policy may result in a denial of access to data and a cessation of collaborative support. In addition, presentation or submission of

unapproved manuscripts puts the investigator at risk of disciplinary proceedings by the CKiD SC and/or funding agencies.

Publications and presentations shall be in compliance with the rules and procedures of the disclosure set forth in the Privacy Act. Confidential or proprietary information shall not be disclosed without the prior written consent of the individual or institution. Privacy Act compliance and documentation of written disclosure consents are the responsibility of each institution involved in the paper/presentation.

22.3.9 Study Acknowledgements

All manuscripts should acknowledge that the data were collected through the CKiD Study and credit participating institutions (CKiD representatives, KIDMAC and the NIH). NIH support contract numbers are to be on the front page of the manuscript. 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, PhD), Central Biochemistry Laboratory (George Schwartz, MD) at the University of Rochester Medical Center, and data coordinating center (Alvaro Muñoz, PhD) at the Johns Hopkins Bloomberg School of Public Health. The CKiD Study is supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, with additional funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01-DK-66143, U01-DK-66174, U01DK-082194, U01-DK-66116). The CKiD website is located at <http://www.statepi.jhsph.edu/ckid>.

22.3.10 Outside Analysis

If data analysis was not carried out at KIDMAC, the lead author is responsible for sending computer programs and associated data sets to KIDMAC.

The programs and data should be labeled table1.dat, table1.sas (if SAS was used for table1) whereby running table1.sas on table1.dat will produce the statistics presented in table 1 of the paper. Data received from KIDMAC should be kept confined to the specific aims of the analysis proposed.

22.3.11 PubMed Central Reference Number (PMCID) Requirement

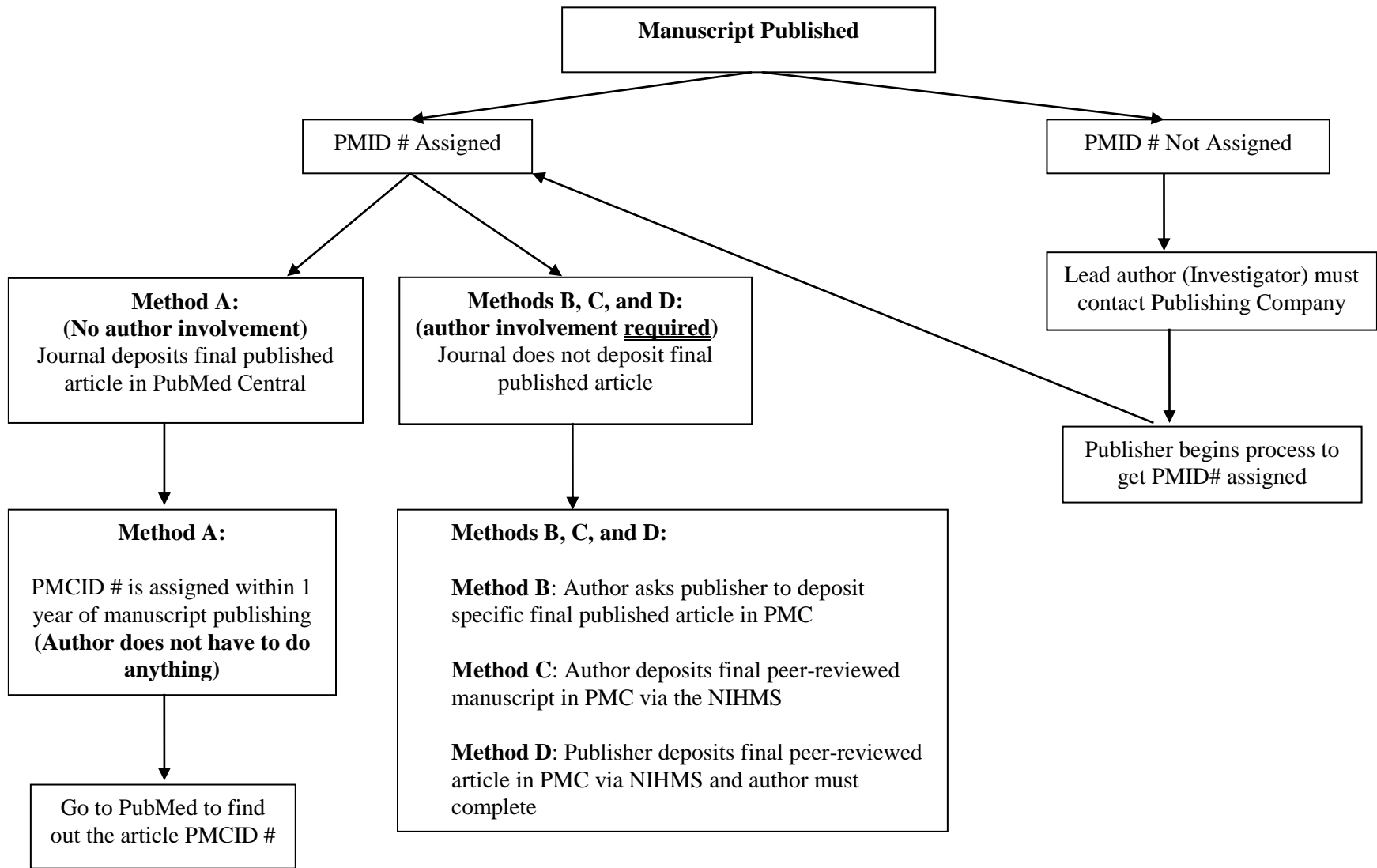
22.3.11.1 Overview of the National Institutes of Health Public Access Policy

The majority of information contained in Section 22.3.11 was adapted from the National Institutes of Health (NIH) Public Access website: <http://publicaccess.nih.gov/>.

NIH implemented the Public Access Policy on January 11, 2008. As of April 7, 2008, all final peer-reviewed manuscripts arising from NIH funds must be submitted to PubMed Central (PMC) upon acceptance for publication. As of May 25, 2008, NIH applications, proposals, and progress reports must include the PubMed Central reference number when citing a paper that falls under the policy and is authored or co-authored by the investigator, or arose from the investigator's NIH award.

There are four submission methods, methods A-D as outlined in Diagram 1 and described in Section 22.3.11.2, to ensure that an applicable paper is submitted to PubMed Central in compliance with the NIH Public Access Policy. **It is the sole responsibility of the author and/or the publishing company to follow the steps to obtain a PMCID #.**

Diagram 1: Process to obtain PMID# for published manuscript



PMID- PubMed reference number

PMCID- PubMed Central reference number

22.3.11.1.1 The Difference between a PMCID and a PMID

The PubMed Central reference number (PMCID) is different from the PubMed reference number (PMID). PubMed Central is an index of full-text papers, while PubMed is an index of abstracts. All CKiD publications should have both numbers. The PMCID number indicates compliance with NIH's Public Access Policy.

In order for a manuscript to be deposited in PMC, a **PMID # must be assigned by the publisher**. In most cases, the PMID # is automatically assigned by the publisher; however, in some cases, the lead author must contact the publisher and request that the PMID # is assigned. See section 22.3.11.1.4 on how to identify a submission method.

22.3.11.1.2 Locate the PMCID

The PMCID is posted in PubMed when an article has been processed by PubMed Central. PMCIDs are listed in the lower right hand corner of the Abstract View in www.pubmed.gov.

The screenshot shows the PubMed Central interface. At the top, there are navigation links for 'NCBI Resources' and 'How To'. Below that is the 'PubMed.gov' logo and a search bar containing 'PubMed' and the PMCID 'PMC2653687'. There are also links for 'RSS', 'Save search', and 'Advanced'. Below the search bar, there are 'Display Settings' (set to 'Abstract') and a 'Send to' dropdown menu. The main content area displays the citation: 'J Am Soc Nephrol. 2009 Mar;20(3):629-37. Epub 2009 Jan 21.' followed by the title 'New equations to estimate GFR in children with CKD.' and the authors 'Schwartz GJ, Muñoz A, Schneider ME, Mak RH, Kaskel F, Warady BA, Furth SL.' The abstract text follows, describing the development of a new GFR estimation formula. At the bottom of the abstract, the PMID '19158356' and PMCID 'PMC2653687' are listed, with the PMCID circled in red. There are also links for 'Free PMC Article', 'Publication Types, MeSH Terms, Substances, Grant Support', and 'LinkOut - more resources'.

22.3.11.1.3 Include PMCID in Citation

When submitting an application, proposal, or report to the NIH, CKiD papers must include the PMCID number at the end of the citation. Any publication that uses CKiD data and does not have a PMCID number is considered to be non-compliant by NIH. It is the responsibility of the lead author of a publication to ensure that it is assigned a PMCID number.

Below is an example of how to cite a paper with a PMCID number.

Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New Equations to Estimate GFR in Children with Chronic Kidney Disease. *J Am Soc Nephrol* 2009;20:629-37. (Commentary by Lemley, KV in *Nature Reviews Nephrology* 2009;5:310-1). PMCID: PMC2653687

22.3.11.1.4 Identify a Submission Method

The NIH Public Access website http://publicaccess.nih.gov/submit_process_journals.htm provides a list of journals that make the final published version of all NIH-funded articles available in PubMed Central (PMC) no later than 12 months after publication. The listed journals deposit these articles in PMC at the time of final publication, which fulfills the submission requirement of the NIH policy without author involvement. The start date shown for each journal is the earliest publication date that meets this requirement. For any journal that is not on the Public Access website's list, see the other submission options outlined under http://publicaccess.nih.gov/submit_process.htm.

The four journals listed below, in which the CKiD study has published articles, follow method A. Specifically, these journals deposit all final published articles to PMC without the authors involvement.

- American Journal of Epidemiology (AJE)
- Clinical Journal of the American Society of Nephrology (CJASN)
- Journal of the American Society of Nephrology (JASN)
- Pediatrics

The journals listed below, in which the CKiD study has published articles, use **other submission options (i.e., method B-D)**. Details about each method is described in Section 22.3.11.2: Submission Methods. Below the name of each journal is a link to the journal's submission method. For examples of copyright agreement forms for each journal is also provided the appendices.

- American Journal of Kidney Disease (see Appendix A for example of copyright agreement) <http://www.ajkd.org/content/edpolicies#nih>
- Epidemiology (see Appendix B for example of copyright agreement) <http://journals.lww.com/epidem/ layouts/oaks.journals/nih.aspx>
- Hypertension (see Appendix C for example of copyright agreement) <http://journals.lww.com/jhypertension/ layouts/oaks.journals/nih.aspx>
- Journal of Urology (see Appendix E for example of copyright agreement) http://www.elsevier.com/wps/find/journaldescription.cws_home/706695/authorinstructions
- Kidney International (see Appendix F for example of copyright agreement) <http://www.nature.com/authors/policies/license.html>
- Mental Retardation Developmental Disabilities Research Reviews (see Appendix G for example of copyright agreement) <http://www.wiley.com/WileyCDA/Section/id-321171.html>
<http://media.wiley.com/assets/1540/86/ctaaglobal.pdf>
- Pediatric Nephrology (see Appendix H for example of copyright agreement) <http://www.springer.com/open+access/authors+rights?SGWID=0-176704-2-994122-0&changeHeader>

22.3.11.2 PMCID Submission Methods

There are four methods to ensure that an applicable paper is submitted to PubMed Central in compliance with the NIH Public Access Policy. Authors may use whichever method is most appropriate for them and consistent with their publishing agreement. Click on the method in the table for details.

Overview of Submission Methods

Version of Paper Submitted	Final Published Article	Final Peer-Reviewed Manuscript
Submission Process	Publisher posts the paper directly to PMC	Papers are required to be submitted via the NIHMS upon acceptance for publication . Publishers, authors or their designee deposit files to the NIHMS and the NIHMS converts them to the PMC native format.
Submission Method to Deposit Files	<p>Method A: Some Journals automatically post NIH supported papers directly to PMC</p> <p>Method B: Authors must make special arrangements for some journals and publishers to post the paper directly to PMC</p>	<p>Method C: Authors or their designee must submit manuscripts to the NIHMS</p> <p>Method D: Some publishers will submit manuscripts to the NIHMS</p> <p>Awardees are responsible for ensuring manuscripts are submitted to the NIHMS upon acceptance for publication</p>
Approve Submission	Publisher	Author, via NIHMS
Approve PMC web version	Publisher	Author, via NIHMS
Responsible Party	NIH awardee	NIH awardee
To cite papers, from acceptance for publication to 3 months post publication	PMCID or “PMC Journal- In Process”	PMCID or NIHMSID
To cite papers, 3 months post publication and beyond	PMCID	PMCID

Method A: Publish in a journal that deposits *all* final published articles in PubMed Central (PMC) without author involvement.

Some journals automatically deposit all NIH-funded final published articles in PubMed Central, to be made publicly available within 12 months of publication, without author involvement. For a list of journals that automatically deposits final published articles to go:

http://publicaccess.nih.gov/submit_process_journals.htm.

Method B: Make arrangements to have the publisher deposit a *specific* final published article in PubMed Central.

Some publishers will deposit an individual final published article in PubMed Central upon author request, and generally for a fee. For the list of publishers that will deposit published article after author's request go to: http://publicaccess.nih.gov/select_deposit_publishers.htm.

Method C: Lead author deposits the final peer-reviewed manuscript in PubMed Central himself/herself via the NIH Manuscript Submission System (NIHMS).

Submitting a final peer-reviewed manuscript to PMC via the NIHMS involves three tasks, as explained below. **Task 1** may be done by an author or by someone in the author's organization (e.g., an assistant or a librarian). **Tasks 2 and 3 must be done by the author.**

A Note on Timing: NIH awardees are responsible for ensuring that manuscripts are submitted to the NIHMS upon acceptance for publication and that all NIHMS tasks are complete within three months of publication.

A video of this process is posted on the NIH Public Access website, click on "Submitting an Article to PubMed Central (WMV Video - 12:01)" at http://publicaccess.nih.gov/submit_process.htm#c.

Task 1: Deposit Manuscript Files and Link to NIH Funding

Upload a copy of the accepted final peer-reviewed manuscript and associated files (e.g., Microsoft Word document and figures) via the NIHMS (www.nihms.nih.gov). At the same time, identify the NIH funding associated with the manuscript. It usually takes less than 10 minutes to complete this task.

Please note that in order to electronically upload a copy of the accepted manuscript and associated files, the author must have one of the following accounts:

- eRA Commons (for NIH Extramural principal investigators, grantees or applicants)
- NIH Login (for Intramural NIH scientists and staff)
- HHMI Login (for HHMI-funded investigators)
- My NCBI (for third party submitters)

In most cases, the CKiD authors will log in to NIHMS using their eRA Commons login or their NIH login. The eRA Commons is an online interface where signing officials, principal investigators, trainees and post-docs at institutions/organizations can access and share administrative information relating to research grants.

Using eRA Commons, follow the steps below to upload the manuscript and files.

Step 1: Choose a login route:

- Select eRA Commons
- Log in with your NIH Commons user ID and password. Once logged in, you will be able to upload your manuscript to the NIH Manuscript Submission System.
- If you need to create a new account, contact your central grants administration within your institution/department.

Note: Before moving to Step 2, please have ready grant numbers, manuscript files(in any electronic word-processing format) and figures. You will need to add all the CKiD grant numbers (U01 DK082194, U01 DK066174, U01 DK066143, U01 DK066116) and any other grants associated with the manuscript

Step 2: Upload manuscript

After providing basic information about the manuscript and contact information, users can upload their manuscript file(s). The system will generate a receipt of the uploaded files in PDF format. The PDF Receipt summarizes the information entered into the system, and merges the manuscript's files into one viewable document. Submitters confirm that the manuscript and any additional supporting documents have been successfully received by NIHMS.

Below are the specific steps you will need to complete to upload a manuscript to NIHMS.

Log into NIHMS and choose “submit new manuscript”

Enter the manuscript title, search in PubMed or find citation in my NCBI Bibliography

Enter Funding Information

1. Title Information
2. Add Funding
3. Upload Files
4. Check Files
5. Set Reviewer & Embargo

Search by:

AND/OR

Search Results:

Grantee/PI	Select	Grant/Project ID	Title
Alvaro Munoz	<input type="checkbox"/>		
Susan L. Furth	<input type="checkbox"/>		
Bradley Warady	<input checked="" type="checkbox"/>	U01 DK066143	Chronic Kidney Disease in Children (CKD III) Other known titles: Chronic Kidney Disease in Children (CKD) Chronic Renal Insufficiency in NAPRTCS Patients

How can I add funding support?

What if I can't find my project or grant?

What if I'm depositing on an author's behalf and don't know the project or grant?

Upload Manuscript Files

1. Title Information
2. Add Funding
3. Upload Files
4. Check Files
5. Set Reviewer & Embargo

Please upload all files associated with your manuscript, including supplemental files, and move to the next step.

Type	Label	File	Size	Date	Remove
Manuscript		<input type="button" value="Choose File"/> 1_Predictors of Rapid Pr...INAL clean version.docx			<input type="button" value="X"/>
Figure	<input type="text" value="Figure 1"/>	<input type="button" value="Choose File"/> Predictors of Rapid Progression - Figure 1.docx			<input type="button" value="X"/>
Table	<input type="text"/>	<input type="button" value="Choose File"/> No file chosen			<input type="button" value="X"/>
Supplemental	<input type="text" value="Appendix"/>	<input type="button" value="Choose File"/> Online Supplementary Ap...ssion paper FINAL.docx			<input type="button" value="X"/>
Figure	<input type="text" value="Figure 2"/>	<input type="button" value="Choose File"/> Predictors of Rapid Progression - Figure 2.docx			<input type="button" value="X"/>
Figure	<input type="text" value="Figure 3"/>	<input type="button" value="Choose File"/> Figure3_PredictedProfiles_022215.pdf			<input type="button" value="X"/>

Add another [Manuscript](#), [Figure](#), [Table](#), [Supplemental](#)

Review PDF

Predictors of Rapid Progression of Glomerular and Nonglomerular Kidney Disease in Children and Adolescents: The Chronic Kidney Disease Cohort Study
Journal: [Am J Kidney Dis](#) PubMed # 25799137 NIHMSID 695825 [Provide citation](#)

1. Title Information

2. Add Funding

3. Upload Files

4. Check Files

5. Set Reviewer & Embargo

Please open and review the PDF Receipt to confirm that you have provided all the materials that make up your manuscript and that are referenced in the text, including any placeholders for supplemental files (if applicable).

You must review the PDF receipt file to advance to the next step.

 PDF Receipt [2015-05-29 10:52:13, 454.5 KB]

Please return to Upload Files if any files are missing.

Save & Exit

Cancel Submission

◀ Upload Files

Set Reviewer & Embargo ▶

Set Reviewer and Embargo

Set Reviewer

Select	Reviewer
<input type="radio"/>	Me (Lucy Mulqueen)
<input type="radio"/>	Alvaro Munoz
<input type="radio"/>	Susan L. Furth
<input checked="" type="radio"/>	Bradley Warady
<input type="radio"/>	George J. Schwartz
<input type="radio"/>	<input type="text" value="First Name"/> <input type="text" value="Last Name"/> <input type="text" value="Email"/>

Set Embargo

The embargo will be set by the designated Reviewer.

Save & Exit

Cancel Submission

◀ Check Files

Send to Reviewer ▶

Task 2: Authorize NIH to Process the Manuscript

If the person who uploaded the manuscript is not the lead author/principal investigator (PI), an email will be sent to the author/PI to approve the PDF and indicate the release date when the manuscript will be made publicly available on PMC. Specifically, the author designates the number of months after publication when the manuscript may be made publicly available in PMC. The author then confirms, via the NIHMS, a statement that the deposit of the manuscript is consistent with any publication and copyright agreements, and that NIH may begin processing the manuscript for use in PMC.

Task 3: Approve the PMC-formatted Manuscript for Public Display

The NIHMS will convert the deposited files into a standard PMC format (i.e., XML-standardized digital format used by PMC). After the conversion process, a preview of the article as it will appear in PubMed Central is emailed to the author, allowing the author to correct any errors if necessary. After final approval, the article will be publicly accessible through PubMed Central (after the time-delay specified by the author.)

Following completion of Task 3:

- The NIHMS will email the author and all PIs the citation with the PMCID once it is assigned;
- PMC will automatically make the paper publicly available after the designated delay period has expired.

For further questions or comments regarding the NIHMS System, please contact the [NIHMS Help Desk](#).

Additional information regarding the NIH Public Access policy can be found at the [NIH website](#), or contact PublicAccess@nih.gov.

Method D: Complete the submission process for a final peer-reviewed manuscript that the publisher has deposited in the NIH Manuscript Submission System (NIHMS).

In a variation of Method C, some publishers deposit the manuscript files in the NIHMS, provide contact information for a corresponding author, and designate the number of months after publication when the paper may be made publicly available in PMC.

A Note on Timing: Though a publisher may make the initial deposit of files under Method D, NIH awardees are responsible for ensuring that manuscripts are submitted to the NIHMS upon acceptance for publication and that all NIHMS tasks are complete within three months of publication.

The NIHMS will notify the author when the manuscript files are received from the publisher. At that point, the author must complete Task 2 (Authorize NIH to process the manuscript) and Task 3 (Approve the PMC-formatted manuscript for public display) as outlined above.

Following completion of Task 3:

- The NIHMS will email the author and all PIs the citation with the PMCID once it is assigned;
- PMC will automatically make the paper publicly available after the designated delay period has expired.

For a video demonstrating author tasks on the NIHMS for Method D, click on “[Approving Submission of an Article to PubMed Central](#) (WMV Video - 6:26)” at http://publicaccess.nih.gov/submit_process.htm#c.

22.4 PROCESS FOR SECONDARY AND ANCILLARY PUBLICATIONS

Secondary publications refer to investigations using data collected as part of the core CKiD protocol but which are not directly related to the hypotheses of the CKiD research. (See Section 1 of the Manual of Procedures for the CKiD core research questions.) While the primary CKiD hypotheses shall have priority in terms of data analysis, proposals to study other scientific questions using CKiD data are encouraged. (CKiD members and Institute staff may propose such studies on their own behalf or on behalf of other qualified investigators from their own or other institutions.) These studies will generally fall into three categories: a) secondary studies among investigators from each of the sites utilizing pooled CKiD data, b) ancillary studies that use study data in conjunction with data from individuals who are not participants in CKiD, and c) site-specific data which does not substantively involve the pooled CKiD data (although some CKiD-gathered demographic or clinical information relevant to local data might be used). These will be considered separately.

1. Secondary studies (see 22.4 for definition) require SC approval. The proposing investigator will follow the guidelines outlined in Section 22.3.2. The SC review of such plans should assure that the study will not interfere with the conduct of the core studies, and that publications arising from the study will not compete with or conflict with similar reports from CKiD primary investigations (as previously defined). A timetable for analyses of the data by KIDMAC will be approved by the SC, taking into account other analyses and data management priorities.
2. Ancillary investigations that use study data in conjunction with data from individuals who are not participants in the CKiD must seek approval from the CKiD SC. The proposing investigator will follow the guidelines outlined in Section 22.3.2. The SC review of such plans should assure that the ancillary study will not interfere with the conduct of the primary or secondary studies, and that publications arising from the ancillary study will not compete or conflict with the reporting of the core or secondary findings of the CKiD data. A timetable for analysis of the data by KIDMAC will be approved by the SC, taking into account other analyses and data management priorities.
3. Site-specific studies must also be reviewed and approved by the SC. Site-specific proposals must have the approval of the principal investigator of the site(s) at the time of submission of the concept sheet. Site-specific proposals which use central laboratory specimens require review by the chair of the Laboratory/Specimen Working Group. In addition, those proposals which require analyses at KIDMAC will require the approval of the KIDMAC PI.

The results of the analysis of specific aims (see Section 1 of the Manual of Procedures) using site-specific data shall not be presented or published prior to their analysis and publication for the entire CKiD cohort, unless approved by the SC.

4. Final abstracts, presentations, and publications of secondary and ancillary studies must also be approved by the SC and receive NIH notification before any presentation to a formal scientific meeting or prior to submission for publication. These requests will follow the same approval process as outlined in Sections 22.3.7 and 22.3.8, and will be accomplished in a timely fashion. The review will focus on the accuracy of the description of the methods and on the conclusions as consistent with the spirit of the CKiD.

22.5 OUTSIDE COLLABORATORS

In some instances, collaborators who are not members of CKiD SC or partner organizations will be involved in data and/or laboratory analyses. These collaborators will be required to acknowledge that CKiD specimens and laboratory data are the property of CKiD. Collaborating scientists will be encouraged to raise relevant scientific questions beyond the data analysis as contracted by the CKiD study; however these requests for approval for data analysis, presentation, or publication must follow the principles outlined in the Publication Policy. Outside investigators should name a CKiD contact person whose responsibility is to ensure the lead investigator has had the opportunity to share his/her ideas with the working groups. Proposals will be submitted electronically to KIDMAC for posting and review. Proposals will follow the same review process as outlined in Section 22.3. Assignment of the writing chair and authorship will follow similar guidelines. For reports resulting from methodological work that exclusively utilizes laboratory data, the collaborating laboratory scientist will have significant input into the assignment of the writing committee and of authorship. However, reports which utilize clinical and laboratory data will likely include authorship of investigators based in CKiD. Analysis of laboratory data from CKiD participants limited to an individual site shall not be published or presented prior to the submission for publication of studies of the core research questions using pooled data.

The expectations and responsibilities of outside investigators are:

- Review and sign response indicating agreement to follow the CKiD Publication Policy.
- Disseminate results to CKiD collaborators in a timely manner. Even though not all studies will result in publication or presentation, all studies from outside investigators should be summarized and presented to CKiD in a written form.
- Before receiving CKiD samples or data, sign a document indicating that the samples and data will only be used as agreed upon in the collaboration. This will be documented at completion of the study. When a study is complete, remaining samples and other agreed upon deliverables must be returned to CKiD.
- Outside investigators will forward agreed upon data to KIDMAC as described in section 22.3. These data will then be entered into the CKiD database where they can be used as part of other analyses after the initial collaborative analyses are completed.
- CKiD investigators have the option to publish results of the analyses if the outside investigator does not wish to write up the study, but agrees that a publication is worthwhile.

22.6 DEPARTING INVESTIGATORS

Departing investigators or staff from KIDMAC or Institute Program Offices shall submit a proposal for authorship role on abstracts and/or papers to CKiD for approval, based on the following guidelines:

- There will be a maximum time limit of two years from separation from the institution to submission of abstract/paper;
- The departing individual can only petition for authorship on abstracts and/or papers in process at the time of separation;
- The departing individual must meet all reasonable criteria for authorship as outlined in the requirement of the journal and as judged by the CKiD SC; and
- A current individual and a departing individual from the same institution may, if appropriate, co-author a single abstract or paper.

22.7 REVISIONS TO PUBLICATION POLICY

Review of the Publication Policy is periodically done by the voting members of the CKiD Steering Committee.

II. PUBLICITY POLICY

A. LOCAL PUBLICITY

Local publicity refers to media distributed primarily to each site's city, metropolitan area, or state. This would include local TV stations, radio stations, and newspapers; city, county, or state health department newsletters; hospital publications; and local university publications not available by general public subscription.

1. Each site can independently release to local media general information about the CKiD study as well as specific information about the conduct of the CKiD study at that site.
2. No disclosures of single- or multi-site study data or analyses should occur without prior clearance by the SC.

B. REGIONAL/NATIONAL PUBLICITY

National publicity refers to media distributed widely outside each site's city, metropolitan area, or state. This includes network television (including "superstations"), network radio, major newspapers, national newsletters (e.g., Nephrology Newsletter), and widely disseminated university publications.

Because such national publicity is likely to impact other sites and the overall reputation of the CKiD study, any site contacted by national media must notify at least one principal investigator at each CKiD site and cooperating federal agencies.

No disclosure of single- or multi-site study data or analyses should occur without prior clearance by the SC.

C. GENERAL GUIDELINES

1. If significant questions arise about other sites or funding agencies ("How much is XIX agency spending overall on the CKiD study?"), refer the reporter to the appropriate agency (i.e., investigators at those sites or agencies).
2. When answering questions, make clear distinctions between personal opinions and positions which have been arrived at jointly by the CKiD collaborators.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 23: QUALITY CONTROL

23.1 QUALITY CONTROL INTRODUCTION

In addition to the quality control methods and programs routinely used at clinical site laboratories and central laboratories, quality control mechanisms for the CKiD Cohort Study are outlined in this section and elsewhere in the CKiD Study Protocol and other sections of the CKiD Cohort Manual of Procedures.

23.2 TRAINING

23.2.1 Investigators and Study Coordinators

The DCC will assist and oversee the clinical coordinating centers to conduct training meetings for study investigators/study personnel to review study design, consent procedures, patient recruitment and enrollment, data collection forms and schedule, test procedures and reporting. All new coordinators who replace existing coordinators will be trained at their clinical sites and/or by their respective CCC.

All investigators are expected to be actively involved in study activities at their clinical site, in study-wide committees (as assigned), and in meetings of the Steering Committee, if applicable. Any investigator and study coordinator who measures blood pressure, Echocardiographs, or carotid IMT must be initially trained and certified and must keep his/her certification up to date.

23.2.2 Data Entry Specialist

Initially, the DCC will train data management staff from the clinical coordinating centers and the central laboratories (i.e., CBL ECHO) on the use of Nephron, the web-based data management system. Subsequently, new employees at the clinical coordinating centers and central laboratories will be trained by existing staff. Nephron is menu driven. The DCC recommends data entry be performed by the same person or people; these individuals should be familiar with all CKiD forms.

23.2.3 Clinical Site

Each clinical site is to be certified in use of the ABPM device and ECHOs. This is described in Sections 17-21 of this Manual of Procedures.

23.3 REPOSITORIES

Quality control procedures carried out within the repositories are described in "Sample Collection and Handling" Section 11 of this Manual of Procedures.

23.4 CENTRAL BIOCHEMISTRY LABORATORY (CBL)

The Central Biochemistry Laboratory has an internal quality control system that was established prior to analyzing any CKiD or CKiD Cohort samples.

This system includes:

1. The inclusion of at least two known quality control samples; the reported measurements of the quality control samples must fall within specified ranges in order to be certified as acceptable.
2. Calibration at FDA approved manufacturers' recommended schedules.

Coordinators and site-designated personnel were trained by the CBL Senior Health Project Coordinator. For each visit, the site coordinator receives a subject-specific kit containing an instruction sheet, a GFR visit flow sheet (if applicable), and the appropriate tubes, vials, containers and sample collection material needed to collect and process samples for the specific visit. The CBL has worked with Diamond Contract Manufacturing to insure that all shipments are in compliance with IATA guidelines for diagnostic specimens. Shipments are sent via Fed Ex, and each kit includes a preprinted Fed Ex airbill for return shipment of samples to the CBL. Shipments are tracked on the Fed Ex website to assure proper delivery in both directions.

Upon receipt to the CBL, each sample is inspected for hemolysis and leakage. This information is logged into an Excel spreadsheet, and if applicable the tubes are hand-delivered to the appropriate lab for analysis of iohexol. For iohexol samples, iohexol concentrations are measured by HPLC; results are copied and pasted into an Excel spreadsheet and sent via electronic mail to the CBL where they are evaluated for iohexol contamination of the baseline blood draw (B0), discrepancies in obvious plasma disappearance at the designated time points, or apparent intravenous catheter infiltration. Any of these instances are reported to the site coordinator and the DCC by electronic mail. If there are no obvious discrepancies, the results are entered into the CKiD web-based database.

23.5 AMBULATORY BLOOD PRESSURE MONITORING CENTER

Coordinators were trained to perform the ABPM procedure at the initial training meeting and at all subsequent annual training meetings. An ABPM training DVD containing a demonstration of proper use and placement of the ABPM and guidelines for family/participant instructions has been distributed to every MW site. A coordinator “cheat sheet” is included in every ABPM shipment, thus readily available to coordinators at the time of placement during the study visit. The “cheat sheet” is also available on the CKiD website (see Section 17 ABPM Cheat Sheet).

Each monitoring is performed for 24 hours with minimum criteria of at least one successful reading per hour for 21 of the 24 hours. Any monitoring with less than 21 clock hours containing at least one successful reading will be deemed a candidate for repeat attempts. Repeat attempts will be determined on a case by case basis with input from study coordinators, MW CCC, and the ABPM coordination center.

Each monitor is downloaded in a timely manner upon receipt by the ABPM Coordination Center. This ensures that the Site Coordinators receive quick feedback on the data collection effort and enables Site Coordinators to make decisions on repeat attempts, clinically important patient feedback, and care strategies. Each downloaded monitor is not erased and re-initialized until data integrity is confirmed in order to avoid the loss of any patient efforts. Downloaded data is analyzed utilizing a proprietary database written in Microsoft Access 2003. This analysis generates metrics in accordance with the

scientific goals of the CKiD study and ensures that each monitoring complies with the goal of at least 21 hours of data for each 24 hour monitoring. The database is located behind a secure firewall on the University of Texas Health Science Center network. Logon requires a network password in order to authenticate to the UT network and requires a second password in order to operate the database. All data is stored on a HIPPA compliant server / NAS drive.

23.6 CARDIOVASCULAR IMAGING CORE RESEARCH LAB (CICRL)

All sites must be certified by the ECHO Imaging Laboratory prior to a V2 study visit in which the first CKiD echocardiogram is performed. The ECHO Imaging Laboratory provides each site with Sonographer training materials. Each site must send a qualification study to the ECHO Imaging Laboratory for verification of correct procedures before certification is granted. A Sonographer Checklist and Self Critique Form (see Sections 19.6.2 and 19.6.3) must be completed for each ECHO prior to submission to the ECHO Imaging Laboratory. Prior to the ECHO being shipped, a copy is made of the forms and the ECHO recording and stored at the site.

Within two business days of FedEx arrival to the Cardiovascular Imaging Core Research Lab (CICRL), each study echocardiogram/vascular ultrasound is logged into the CICRL database. The CICRL database consists of the date the ultrasound was received, the site number and the ID of the patient. The measurements are performed offline using Digiview, proprietary software of Digisonics Inc. If the ultrasound arrives damaged or unmeasurable, the CICRL technical director immediately follows up by email with the individual site requesting a copy of the ultrasound to be resent. The e-mail indicates the reason the ultrasound is unmeasurable and request the site sonographer to contact the technical director of the CICRL for discussion and follow up. All data is stored on a HIPPA compliant server / NAS drive. Each month, the CICRL ultrasound raw data measurement database is emailed to Data Coordinating Center.

23.7 DATA FORMS AND DATA

In the CKiD Cohort Study, each clinical coordinating center's staff members will enter all questionnaire and forms electronically. Data entry staff at the central biochemistry laboratory will enter CBL study test results (i.e., iohexol concentrations and renal panel results). Appropriate edit checks will be in place at the key entry (database) level. Original study forms will be entered and kept on file at the Clinical Coordinating Center.

Any and all paper forms or copies of forms (i.e., copies of ECG strips, questionnaires) that pertain to the CKiD study are to be filed in the participant's file in a logical and consistent manner to provide accessibility for the duration of the study. Participant files are to be stored in numerical order and stored in a secure and accessible place and manner. Participant files will be maintained in storage for a period of 3 years after completion of the study.

23.8 QUALITY ASSURANCE CONFERENCE CALLS AND DATA ENTRY CHECKS

Over the course of the study, we plan to have conference calls with the principal investigators and coordinators to review recruitment and data quality. The DCC will also review data entry forms for quality control. A subset of the forms that have been data entered will be requested from each clinical coordinating center. When a form is selected, the Clinical Coordinating Center staff will pull that form, copy it and send the copy to the DCC for review.

23.9 QUALITY CONTROL OF THE DATA COORDINATING CENTER

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.

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.

Data entry forms are designed to be similar to the paper version to facilitate data entry.

In each form, KID ID, visit, version date, data entry person, and date of data entry will be automatically filled in by Nephron. Data entry person and date of data entry are not on the paper forms, but are recorded by Nephron.

1. Skip Patterns: Nephron has skip patterns programmed into it to match those on the paper forms. When a skip pattern moves from one field to another, skipped fields are automatically filled with "-1".
2. Many forms require records to be unique. Duplicate records will generate error messages when the record is submitted to the database. The duplicate record based on key fields will not be placed in the database.
3. Nephron will not permit blanks to be left in any field on any data entry form except the MAT form. The user will not be able to save a record until all fields have been filled out. This will require data entry personnel to use "-7" (Refused), "-8" (Don't Know), or "-9" (Missing) to indicate absent data.
4. Range checks: Categorical variables (that is, where response is 1, 2 ...) have been supplied with soft validations. Thus, upon an invalid entry, a validation error box will open informing the user that the value is outside of the specific range. By selecting **Re-Enter Value**, the user can re-enter the field's value. By selecting **Override**, the user can choose to keep the original value, which will be logged in the system. Nephron will open a printable screen listing all such values when the **Submit Data** button is selected. Once printed, this list can be sent to the appropriate personnel for resolution. Edit reports for out of range values, inconsistent answers, and other areas of interest will be available in Nephron for use at the local site for information and 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. The same edit procedure will be followed every 12 months so that a clean historical data set can be generated on an annual basis.

Below is a description of the data that will be edited, the types of edits that will be generated, and the procedures sites should follow to respond to these edits.

1. Data to be edited. All data that has been entered in a given visit's calendar time period may be subject to this annual edit process.
2. Types of Edits. The types of edits generated in this process may include:
 - a. Range checks: a range edit indicates that a value has been entered for a variable that is out of the valid range defined for that particular variable.
 - b. Skip pattern checks: this type of edit is generated either when 1) a value has been entered into a field that other data have indicated should have been skipped due to a defined skip pattern; or 2) a field has been skipped that should have had a value entered.
 - c. Internal Consistency Checks (ICC): These checks generate edits when there are inconsistent answers for a participant internal to one form.
 - d. Cross Form Checks (CFC): CFCs look for consistency between different sections of some of the longer forms, between forms and sub-forms, and between different forms containing related data.
3. Procedures for Resolving Edits. Edits generated offline and distributed to the sites on paper will be resolved using the online Nephron edits system – modifications to existing values can be accomplished through the “View Data” or “Modify Data” options on the Apollo data menu and confirmation of existing values can be accomplished using the “Confirm Edits” option on the data menu.

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.

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.

23.10 SECURITY AND BACK-UP OF DATA

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 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.

23.11 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 CASE IDs 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 all dates; (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.

23.12 DCC SUMMARY ANALYTICAL FILES

Data will be periodically frozen for construction of analytical data files. To standardize the analysis of such complex data and reduce the likelihood of software coding errors, we have and will continue to develop common summary data files, derived from the web-based database, for analyses. 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, CIMT, GROWTH, MEDSUM, LABMARKERS) 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.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 24: DATA MANAGEMENT

24.1 NEPHRON

The DCC will continue to develop a web-based data management system (nicknamed Nephron). Nephron is centrally based, that is, the programming code and data are stored in a central location at KIDMAC and accessed through Internet Explorer. Nephron is used for:

- Data entry
- Data modification
- Report generation
- Tracking study forms
- Creating visit control sheets for upcoming appointments
- Tracking sub-study information

Nephron forms have been designed to be similar to the paper copy to lessen the learning curve for the clinical sites. While data will be stored centrally, the user interface will be familiar to most computer users and commonly used mouse and/or keystroke combinations are utilized in the system.

Notification of scheduled downtime for system updates will be emailed to the two Clinical Coordinating center's (CCCs) Project Directors. Each CCC will be responsible for disseminating this information to their designated clinical sites.

In case of a server failure or loss of Internet connection to outside sites, KIDMAC will notify each CCC's contact person by fax, providing information on any problems and the status of the fix. Each CCC will be responsible for disseminating this information to their designated clinical sites.

24.1.1 System Requirements

The Nephron system requires Internet Explorer 6.0 (IE6) web browser and (preferably) high-speed Internet access. CCCs should only use the browser supplied by KIDMAC; upgrading to a browser beyond Internet Explorer 6 may cause unexpected problems using Nephron.

Unblock the Internet Explorer Pop-up blocker by performing the following steps:

- **Select the Tools menu bar**
- **Select Pop-up blocker settings**
- **Enter the Nephron website in the space provided to allow pop-ups**
<https://statepiaps.ihsph.edu/nephron/groups/aspproc/>
- **Select the Add button and close the window**

24.1.2 Accessing Nephron

Nephron may be accessed from <https://statepiaps.jhsph.edu/nephron/groups/aspproc/>, where you will be asked to log into the system. Please note that you must use a secure web browser (128-bit) to access the site.

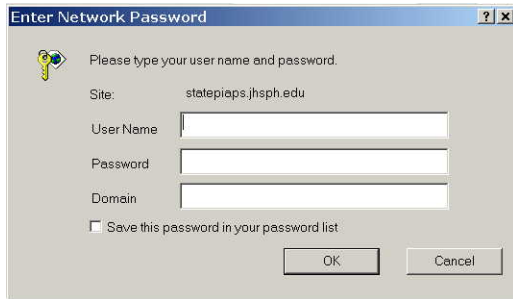


Figure 1

In the **Enter Network Password** window (see Figure 1), enter your KIDMAC assigned userid and password in the appropriate fields. Some users may find it necessary to enter **statepiaps** in the Domain Field. Click on **OK** to go to the Navigation menu. For security reasons, do not click on “Save This Password in your password list”. If you have trouble logging in, contact KIDMAC.

24.1.3 Navigation Menu

The Navigation Menu provides access to all aspects of Nephron, including data entry/editing and report generation. The following table gives a brief description of each option in the Navigation Menu:

Menu Item	Description
Home	Displays a brief description about Nephron, CKiD and KIDMAC.
Data Menu	Allows you to enter or modify data, generate reports, and download data.
Report Menu	Provides a list of reports in Nephron.
KIDMAC admin	KIDMAC-only access for Nephron administration
Forms with Variable names	Provides the forms with variables names included.

24.1.4 Entering Data

- From the **Navigation Menu**, select **Data Menu**. Choose **Enter a Form** from the dropdown list of items to do and click **Submit** button.
- Select from, KID ID and visit and click the **Submit** button to access the form.
- After entering the form data, click **Submit Data** to add the record to the database.
- Confirm record has been added to Nephron when the message “Record Successfully Added” appears.

Nephron uses a form entry system that displays the form in its entirety. For forms larger than the screen display, scrolls bars at the right and bottom of the screen may be used to view the entire form.

Sections of forms that require entry of repeating data (e.g., descriptions of each sibling) are entered on sub-forms, which are linked from within the main data entry form. Sub-forms allow for multiple records per KID ID and visit.

The forms are designed to be similar to the paper version to facilitate data entry. In each form, KID ID, visit, version date, data entry person and date of data entry will be automatically filled in by Nephron. Data entry person and date of data entry are not on the paper forms, but are recorded in Nephron.

A. Field Scrolling and Record Entry

Movement between fields on a form can be done using either the TAB or ENTER keys. Note that using the ENTER key will not enter (or save) the form – that can only be done by clicking on **Submit Data** button at the bottom of the form. A form cannot be saved unless all fields have been completed; Nephron will not allow blanks in fields on any data entry form except the MAT form.

B. Skip Patterns

Nephron has skip patterns programmed, which match those on the paper forms. When a skip pattern moves from one field to another, skipped fields are automatically filled with“-1.” If data has been collected in a section that should be skipped, or if there is an error in the skip pattern, the user can still enter data into fields that were skipped, using the mouse or tab key to position the cursor in the appropriate field and enter the data.

C. Field-Level Validations:

- Many forms require records to be unique. Duplicate records will generate error messages when the record is submitted. The duplicate record based on key fields will not be added to the database.
- Nephron will not permit blanks to be left in any field on any data entry form except the MAT form. The user will not be able to save a record until all fields have been completed. This will require data entry personnel to use “-8” (Don’t Know), or “-9” (Missing) to indicate absent data.
- Dates and times are not automatically filled with “/” and “:” characters, and must be entered along with the numbers. An invalid date or time entry will bring an error message box to the screen informing the user to enter dates in a valid mm/dd/yy or hh:mm format; choosing **OK** will allow the user to re-enter the field entry. A shortcut for entering a time is using a period (.) instead of a colon (:) in the time field; the time entry must have two numbers before and after the period.
- Entering an invalid format (e.g., too many digits, letter instead of number) in a field will bring a Type Conversion Error message to the screen. Choose **Yes** to discard the newly entered value into the field and re-enter the data.
- Categorical variables (that is, where response is 1, 2 ...) have been supplied with soft validations. Thus, upon an invalid entry, a validation error box will open informing the user that the value is outside of the specific range. By selecting **Re-Enter Value**, the user can re-enter the field’s value. By selecting **Override**, the user can choose to keep the original value, which will be logged in the system. Nephron will open a printable screen listing all such values when the **Submit Data** button is selected. Once printed, this list can be sent to the appropriate personnel for resolution. Once the appropriate personnel have responded, you can:
 1. Use the **Modify** option to access the record and modify the value to within range.
 2. Use the **Confirm Edit** option on the data menu to confirm an out-of-range value.

Validations after data entry of the entire form, cross-form validation, and longitudinal validation of forms within an individual ID are not currently implemented in Nephron. Much

of the cross-form validation and longitudinal validation will be done centrally. An advantage of batch edits is that they provide a better understanding of the most frequently generated edits, which will allow KIDMAC to work with the clinical sites to avoid errors during the time data are collected.

To add a record to the database, use the **Submit Data** button located at the bottom of the form. You **must** receive the confirmation message, “Record Successfully Added” after submitting the record to ensure the data has been saved to the database. If you do not receive this message, the record was not added to the database and you should report this to KIDMAC.

After the data have been submitted, use one of the buttons located at the bottom of the form to continue:

Go to Menu	To return to the Navigation Menu.
Enter Form	To begin data entry for a new form and selecting a new ID
Submit	To save the data to the appropriate dataset.

If you choose one of the above options before submitting the record, a message appears, “Form data has not been saved. Press OK to return to the form or CANCEL to exit without saving data.” The user may choose to save the form or continue without saving the data.

24.1.5 Viewing or Modifying Data

There are two ways to view and modify the data in Nephron from the data menu. To view existing data or modify data, select **View Data in Form Format/Update data in Table Format** from the data menu. Then, select the form, KID ID and visit data that are of interest. The form will be opened with visit specific data. If more than one record was retrieved, you will be able to navigate through the records using the following buttons at the bottom of the form:

- << Go to the first record
- < Go to the previous record
- > Go to the next record
- >> Go to the last record

Modifying Data: To change data in this screen, select the **Go to Update Screen** button, to display a tabular format displaying question number, variable name, and existing value for each field. Modify any fields that need to be changed. When you have finished modifying fields, click the **Update** button. Answer OK to the “Update this record?” prompt. A prompt with the updated variable name will be displayed for each variable changed. A prompt that says, “Record Successfully Updated” indicates the changes have been saved in the database. If you do not receive this message, you should assume the changes have not been saved and notify KIDMAC of the error.

To change a value in a primary key field, such as visit, contact the data manager at KIDMAC by email or telephone. Only KIDMAC is able to update primary key fields.

Deleting Data: Historical data (i.e., data that has been cleaned by KIDMAC) cannot be deleted by the clinical sites. Please contact the data manager at KIDMAC by email or telephone to request deletion of a record. Current visit data (i.e., dirty data) may be deleted at the clinical site level.

24.1.6 Generating Reports

To run a report, select “Run a Report” from the data menu and select the report that is of interest. Some reports may require you to enter additional data before they are able to run.

The following reports will be available in Nephron:

Report	Description
GFR Results Report	The GFR Results Report lists the GFR by KID ID for CKiD participants
QA Report	The Quality Assurance (QA) Report monitors the status of data entry for the GFR related forms.
Recruitment Report	The Recruitment Report contains the participants’ estimated GFRs and socio demographic information.
Site Recruitment	The Site Recruitment Report contains the number of children recruited by site name and number.
Visit Control Sheet	The Visit Control Sheet is an administrative report that aids the clinical sites in preparing for a participant’s visit. It indicates sub-studies in which the participant is enrolled, the participant’s completed visit dates, forms to be completed during the participant’s visit, and provides a suggested target date for the participant’s next visit. VCS reports can be printed in batches or individually.
Lipid Lab Variables Report	The Lipid Lab Variables Report lists the lipid panel results by KID ID for CKiD participants.
Selected Renal Panel Lab Report	The Selected Renal Panel Report lists the renal panel results by KID ID for CKiD participants.
Iron Lab Report	The Iron Lab Report lists iron studies results by KID ID for CKiD participants.

24.1.7 Adding a KID ID

All new study participants will need to have a new KID ID registered with Nephron. To do this, select “Add New KID ID” from the data menu and enter the new KID ID with no hyphens, dashes or spaces into the field.

24.1.8 Outcomes

When an event is logged (via GH, MH or DSEN), a record will automatically be added to the MAT table in Nephron that includes a computer-generated tracking number, the event code, event description, KID ID, visit, the form, and question number.

24.1.9 Visit Number

Visit is a numeric field, with Visit 1A corresponding to 10, Visit 1B = Visit 15, Visit 2 = Visit 20, Visit 3 = Visit 30, etc. In Nephron, Visit will be displayed as V1a, V1b, V2, V3, V4 etc. on the Menu and Reports page. However, on the data entry form page, Visit will be displayed as 10, 15, 20, 30, 40 etc.

24.2 SECURITY

It is our intention to ensure that CKiD data is of high quality and secure from external threats. In this section, we detail security mechanisms that Nephron will use to guarantee that CKiD data is not compromised.

24.2.1 Windows 2003 Integrated Authentication

Each individual who uses Nephron will require a user account on the KIDMAC Windows 2000 Advanced Server. We use group permissions and integrated authentication to control access to the server. Authentication and data entry is encrypted using 2048-bit secure sockets layer (SSL) to guarantee that user credentials are not compromised. The SSL security protocol provides data encryption, server authentication, message integrity, and optional client authentication for a TCP/IP connection. It prevents interception of data between the site and the Nephron server.

24.2.2 Clinical Site Specific Data Entry

Each registered user will only be able to edit data from his/her clinical site – users will not be able to enter or change data from other clinical sites. However, data may be downloaded from all clinical sites.

24.2.3 Participant Name/ID Separation

Participant names are never associated with participant ID's in Nephron. No person or computer at KIDMAC has access to participant names, and the data is associated only with KID IDs.

24.2.4 Hardware Integrity and Johns Hopkins Bloomberg School of Public Health Firewall

KIDMAC maintains all of its own hardware within the STATEPI group located in the Department of Epidemiology. System administrator privileges are restricted to a limited number of personnel. Accounts are given only to users who are actively working on STATEPI projects.

All KIDMAC computers are protected by the Johns Hopkins Bloomberg School of Public Health firewall.

While no security is foolproof, by using multiple, state-of-the-art security mechanisms, we hope to prevent any intrusions into the CKiD data.

24.2.5 Security at the Clinical Site Level

Recommended guidelines to ensure the security of the CKiD data:

- Do not share your username with non-CKiD staff.
- Do not share your password with anyone, including other CKiD staff.
- Do not check the “Save this Password” checkbox when logging in to the system.
- Close web browser when not using Nephron.

Clinical sites must immediately notify KIDMAC of position reassignment and newly-hired data management personnel.

24.3 FORMS

KIDMAC will distribute new or updated forms with a new version date via a numbered communication memo. The original form that accompanies the numbered communications memo should be used as a master from which all copies for interviews should be made.

All CKiD forms contain a footer with the date the form was implemented. This date will be considered the current version number of the form. Subsequent changes to forms will be indicated in the footer in one of two ways:

1. In the case of substantial revision to a form (i.e., a change in the data collected or the addition or deletion of variables), the change will be indicated by assigning a new date to the form. For example, if F01 version 01/01/05 were to receive substantial changes, the version date in the footer would change to the date of implementation of the new version (e.g., from 01/01/05 to 01/01/06).
2. In the case of minor revision to a form (i.e., no change in data collected – correction of typo or change in wording), the change will be indicated by adding a letter after the date in the footer. For example, if F01 version 01/01/05 were to receive minor changes, an "a" would be added to the end of the version date in the footer. If F01 version 01/01/05a were to receive subsequent minor changes, the "a" in the footer would be changed to a "b" (e.g., from 01/01/05 to 01/01/05a to 01/01/05b).

See the Form Versions excel file distributed at every visit for a listing of all current CKiD form versions.

DATA ENTRY FORMS AVAILABLE ON NEPHRON

Baseline and Administrative		Follow-up	
Form ID	Form Name	Form ID	Form Name
EL	Eligibility	F12	Follow-up Smoking, Alcohol, Drugs & Physical Activity
REF	Refusal	F13	Follow-up General History
ADVR	Adverse Event Form	F14	Follow-up Medical History
CIF	Contact Information	F16	Sun Exposure
DSEN	Disenrollment	F17	Overall Physical Activity
MV	Missed Visit	F18	Fitness Measurements
PCO	Participant Close Out	L21	Specimen Collection for V2
TRF	Transfer	L31	Specimen Collection for V3, V5, V7...
TRS01	Transitional Form	L41	Specimen Collection for V4, V6, V8...
CBG	Census Block Group Information	L09	Central Laboratory – Lipid Panel Results
F01	Symptoms	L11	Central Laboratory – Cystatin C Results
F02	Smoking, Alcohol, Drugs & Physical Activity	L12	Central Laboratory – Iron Studies Results
GH	General History	L13	Central Laboratory – Vitamin D Results
MH	Medical History	L22	Echo Alert Parameter Form
F15	Nutritional Assessment and Steroid Use		
FFQ	Food Frequency Questionnaire		Shipment Tracking Forms
MAT	Medical Abstraction Tracking	ST01	Shipment Tracking for CBL
MEDS	Medication and Supplemental	ST03a	Shipment Tracking for Serum, Plasma and Urine for NIDDK Repository
PE	Physical Exam	ST03b	Shipment Tracking for Hair and Nails for NIDDK Repository
L01	Specimen Collection for V1a	ST04	Shipment Tracking for Rutgers Cell and DNA Repository
L02	Specimen Collection for V1b	ST05	Shipment Tracking for CBL Dry Ice Shippers
L03	Local Laboratory – Renal Panel Results		
L04	Local Laboratory – CBC Results		Phone/In-Person Follow-up
L05	Central Laboratory – Renal Panel Results	PFU01	Phone/In-Person Follow-up Interview Form
L06	Local Laboratory – Urine Assay	PFU01	Follow-up Site Questionnaire
L07	Central Laboratory – Iohexol Concentration		
L08	Central Laboratory – iPTH and wrCRP		

Neurocognitive/Behavioral Data Entry Forms			
NRC01A	PedsQL - Parent Report for Toddlers (2-4 years)	NRC04A	Behavioral Data Coding Sheet – 12 to < 24 months
NRC01B	PedsQL - Parent Report for Young Children (5-7 years)	NRC04B	Behavioral Data Coding Sheet – >= 2 years to < 6years
NRC01D	PedsQL - Parent Report for Children (8-12)	NRC04C	Behavioral Data Coding Sheet – >= 6 years to < 8 years
NRC01E	PedsQL - Self Report for Children (8-12)	NRC04D	Behavioral Data Coding Sheet – >= to 8 years to < 12 years
NRC01F	PedsQL – Parent Report for Teens (13-18)	NRC04E	Behavioral Data Coding Sheet – >= 12 years to < 18 years
NRC01G	PedsQL - Self Report for Teens (13-18 years)	NRC04F	Behavioral Data Coding Sheet – >= 18 years to < 21 years
NRC01H	PedsQL - Self Report for Young Adults	NRC04G	Behavioral Data Coding Sheet – >= 21 years
NRC03A	Cognitive/Development Coding Sheet – 12 to < 30 months		
NRC03B	Cognitive/Development Coding Sheet – 30 to < 4 years		
NRC03C	Cognitive/Development Coding Sheet – 4 years to < 6 years		
NRC03D	Cognitive/Development Coding Sheet – 6 years to < 17 years		
NRC03E	Cognitive/Development Coding Sheet –17 years and older		

**Italics indicate the form will be available in the near future.*

24.4 PARTICIPANT IDENTIFICATION (ID) NUMBERS

Participant ID numbers for the CKiD are assigned sequentially after the Eligibility Form is completed. The structure of the ID number is as follows:

C- SS-PPP

C:	Cohort Number:	1: participants who are enrolled in the first phase of CKiD recruitment 2: participants who are enrolled in the second phase of CKiD recruitment
SS:	Site Number:	Within each CKiD Clinical Coordinating Center consortium there are clinical sites (hospitals/clinics/institutions) that conduct study visits. During the CKiD start-up phase, Project Directors assigned a number to each clinical site within their consortium. Values between “01” and “49” are reserved for clinical sites coordinated by the Midwest Clinical Coordinating Center, and “50” to “99” for clinical sites coordinated by the East Coast Clinical Coordinating Center.
PPP:	Participant’s number:	The clinical sites will assign each participant a sequential individual number. (The respective Project Directors determined the three-digit ranges based upon the expected number of enrollment at each clinical site.)

All recruits enrolled into the CKiD will be assigned a 6-digit KIDID on the forms.

24.5 TROUBLESHOOTING

If you are experiencing problems with Nephron, please report these problems to KIDMAC.

If you receive one of the following error messages, please try the following steps:

IE5 Error Message: The page cannot be displayed.

- Verify that you have entered the correct website in your browser.
- If you selected a link from the Navigation menu and received this error, the item is not currently available.
- Try to go to another website; if unable to connect to a different site, contact your local Internet provider for assistance, contact your Clinical Coordinating Center Project Director or KIDMAC by email to see if there are problems with Nephron.

Error Message: You have entered a date or time in an incorrect format. You must enter dates in the format MM/DD/YYYY. There must be two digits for the month, data and four digits for the year... You must enter times in the format HH:MM...

- Dates need to be entered in **mm/dd/yyyy** format, with slashes (/) and leading zeros (0).
- Times need to be entered in **hh:mm** format, with a colon (:) and leading zeros (0).
- Select **OK** and choose **Re-Enter Value** from the validation window.

Error Message: You have entered a value outside the normal range for this field. If you would like to confirm this value, please enter a reason for the unexpected value and then press the “override” button. If you have entered the value in error, please press the “Re-Enter Value” button and correct your mistake.

- The value entered in the field is not one of the pre-approved ranges for the field. Select **Re-Enter** to enter a new value or **Override** to accept the out-of-range value.
- If you choose **Override**, you must enter a reason for overriding the value.

Error Message: You do not have a database account. Please contact the Nephron Administrator.

- You need an account to access Nephron. Contact the Data Coordinating Center Project Director, Judith Jerry-Fluker at jjerry@jhsph.edu or 410-614-1277.

Error Message: Sorry, [username] does not have permission to [Enter a Form | View/Modify Data | Run Report | Download Data].

You do not have permission to access the application. Contact your Clinical Coordinating Center.

24.6 VARIABLE NAMES AND CODEBOOKS

Each KIDMAC variable has six characters; the first four are a unique name for the variable and the last two indicate on which form the variable is located. Therefore, all variable names on a given form have the same last two characters. This naming convention allows for longitudinal analyses and eliminates the possibility of overwriting variables when merging datasets.

Documentation describing the structure of the new data was created. A Variable Master File (VMF) is created for each form. The file describes, in a structured format, the name, type, length, description, and range of each variable on that form. A small portion of a VMF file is shown below:

```
Chronic Kidney Disease in Children Cohort Study
Form GH – General History
-----
8 8.0
KIDID = Participant ID
A.1 =
10100010= ID# 10100010|.|.60499999= ID# 60499999
-----
2 2.0
VISIT = Visit number
A.2 =
1= Visit 1|.|.99= Visit 99
-----
6 $
FKEY = Form identifier number
A.0 =
Character
-----
8 $
VERSMH= Form version
A.3 =
01/01/05= January 1, 2005|.|.12/31/08= December 31, 2008
|-1= N.A. (Skipped)|-8= Don't know|-9 or Blank= Missing
```

Additional files are generated from the VMF file by KIDMAC and distributed with the historical data. These files are listed below with their filename extensions and descriptions.

1. Codebook files, *.cdb, data dictionary
2. SAS input files, *.inp, fixed-column SAS input files
3. Index files, *.ndx, condensed version of codebook file

The codebook files are a user-friendly version of the VMF files and are a comprehensive definition of the structure of the data. The columns in a codebook file are listed below in order:

1. Start Column: the column position where the given variable's data begins
2. Field Length: the length of the given variable
3. Field Format: the format of the given variable
4. Variable: the KIDMAC variable name
5. Section/Question: the location of the given variable on the form
6. Description: description of the data the given variable holds
7. Code: range of possible values for the given variable

24.7 OFFLINE EDITING

On an annual basis, KIDMAC will generate site-specific batch edits and distribute these edits to the respective clinical sites. The same edit procedures will be followed every year so that a clean historical data set can be generated and distributed on an annual basis.

Below is a description of the data that will be edited, the types of edits that will be generated, and the procedures clinical sites must follow when responding to these edits.

24.7.1 Data to be Edited

All data that has been entered in a given visit's calendar time period may be subject to this annual edit process.

24.7.2 Types of Edits

The types of edits generated in this process may include:

a. Range checks

A range edit indicates that a value has been entered for a variable that is out of the valid range defined for that particular variable.

b. Skip pattern checks

This type of edit is generated either when 1) a value has been entered into a field that other data have indicated should have been skipped due to a defined skip pattern, or 2) a field has been skipped that should have had a value entered.

c. Internal Consistency Check (ICC)

These checks generate edits when there are inconsistent answers for a participant internal to one form.

d. Cross Form Check (CFC)

CFCs look for consistency between different sections of some of the longer forms, between forms and sub-forms and between different forms containing related data.

Range, ICC and skip pattern edits are sorted by visit number, then by KID ID, and finally by table or dataset (corresponding to one of the CKID forms). All other edits are sorted by form and KID ID.

Basic information obtained from each edit:

- The type of edit generated (duplicate, range, skip, ICC or CFC)
- The exact question number on the form to which the edit pertains
- Brief description of the problem
- Variable name for which the edit was generated and the value contained in the database for this particular variable
- Range edits will also include the valid ranges as they are defined by KIDMAC
- Skip edits will include all variables included in the skip pattern and the values listed for each respective variable.

24.7.3 Procedures for Resolving Edits

Edits generated offline and distributed to the clinical sites on paper will be resolved using the online Nephron edits system – modifications to existing values can be accomplished through the **View Data** or **Modify Data** options on the Nephron data menu and confirmation of existing values can be accomplished using the **Confirm Edits** option on the data menu.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 25: STUDY COORDINATOR

25.1 INTRODUCTION

The CKiD Study Coordinator plays an integral role in the success of the CKiD study. The Study Coordinator works with the Principal Investigator and Co-Investigator at their clinical site to ensure that the entire study runs smoothly and the protocol is being implemented correctly to collect quality data. The Study Coordinator should promote a team approach and work closely with all staff, which may include the following:

- Clinical Coordinating Center (CCC) Coordinators whose responsibility are to oversee each of the sites involved with CKiD
- GCRC and/or clinic staff
- KIDMAC, the Data Coordinating Center (DCC)
- Central Biochemistry Laboratory (CBL)
- Department of Development and Behavioral Sciences and/or Department of Psychiatry to coordinate neurocognitive and behavioral testing
- ABPM Coordinating Center
- Cardiology Department and/or ECHO lab to schedule study echocardiograms
- MRI Department
- Ultrasound lab, if applicable
- Anesthesia, if applicable
- Secretary/receptionist and/or staff whose responsibility it is to schedule participants to maintain adherence to follow up visits within the designated window, if applicable
- Local Institutional Review Board (IRB)
- Contract and Grants office

Study Coordinators will participate in specific training for the CKiD study. At the training sessions, Study Coordinators will be trained in several areas: study design, consent procedures, patient recruitment and enrollment, forms completion, conducting interview assisted questionnaires with participants, ABPM, test procedures (i.e., iohexol GFR and specimen collection and handling), and responding to data discrepancy inquiries. Study Coordinators will be responsible for following and maintaining the CKiD protocol. They (or a designee) are also trained and certified in measuring blood pressure using the Aneroid sphygmomanometers. The Study Coordinator and the Principal Investigator (or designee) from each of the sites will be required to demonstrate proficiency in knowledge of the blood pressure protocol for certification. The training can be completed on-line via the CKiD website (https://statepi.jhsph.edu/ckid/BP_certification.html). At the conclusion of the training, personnel will take a knowledge assessment test and be required to obtain a passing grade of 85%. The Coordinator will practice eliciting information from study participants in a uniform manner.

The Coordinator must be trained and prepared to handle all aspects of the study in the absence of other personnel. If the Study Coordinator should leave the position before the completion of the study, he/she should train their replacement (if possible). New Study Coordinators must receive orientation by the CCC. The CCC Coordinator acts as a liaison between the CCC and the DCC, making sure that needed information reaches the appropriate people.

Each Study Coordinator must be thoroughly familiar with the Protocol and Manual of Procedures and must keep copies current by inserting any revised pages. They are also responsible for maintaining copies of all study correspondence including making sure that all IRB communication and approval are achieved. Maintaining regulatory documents and ensuring that a CKiD file is established for every participant who enters the study is also necessary. The CKiD file for each participant will include a copy of all study forms for each participant and all other pertinent medical history information.

The Study Coordinator is responsible for reporting new participants consented for CKiD, completing and mailing the original study forms corresponding to each study visit to the CCC, and obtaining, processing and shipping specimens according to procedures in a timely and accurate fashion.

25.2 PARTICIPANT INSTRUCTIONS FOR CONSENT AND FOLLOW-UP

Study Coordinators assume the primary role of assuring that participants are instructed in the goals and responsibilities of the CKiD study. This includes making sure that all participants have signed the informed consent and assent (if applicable) at the appropriate time.

Following the signing of informed consent and assent (if applicable), the Study Coordinator will assure that participants are scheduled for all required procedures including, but not limited to: neurocognitive assessments, routine blood pressure testing, ECHO, 24 hour ambulatory blood pressure monitoring, blood and urine laboratory studies and questionnaires. Optional samples include: fingernail, toenail, hair, genetic and biological blood, and urine collection, The follow-up appointment schedule is outlined in the MOP and consent form template and the CCC will provide a guidance regarding visit and specific procedure windows for each participant visit.

25.3 MONITORING

The Study Coordinator must try to maintain a general environment intended to promote retention. Each participant should be given an individualized instructions that contains, but is not limited to, a copy of their signed consent and assent form (if applicable), ABPM instructions, study brochure and schedule of the participant's study visits. Review of this material should be done by the Study Coordinator, or other staff members.

25.4 HOSPITALIZATION AND DEATH PROCEDURES

This study is not a clinical trial; therefore, only documentation of adverse events occurring within 24 hours of a study procedure is required, or any adverse event related to a study procedure. Adverse events are considered any undesirable clinical experience occurring to a patient during or 24 hours after the study. If a participant has a serious adverse event (SAE) related to a study procedure (i.e., Iohexol GFR), the event should be reported by the Study Coordinator to the local IRB (in accordance with the local IRB policy) as well as to the CKiD CCC and the DCC. For the purposes of this study, a SAE 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. If the clinical site becomes aware of the death of a study participant between study visits, local IRB procedures should be followed and the CCC and DCC informed of the event within 5 days.

The Study Coordinator will also be responsible for sending the CCC the corresponding forms and documentation concerning the death that will be data entered by the CCC.

25.5 DIALYSIS/TRANSPLANTATION

It is the Study Coordinator's responsibility to complete the appropriate forms in the event of the need for renal replacement therapy (RRT). Outcome measures are documented in the same fashion.

25.6 ORDERING AND FILING DATA FORMS

The Study Coordinator is responsible for maintaining updated data collection forms to be used by the clinical site. Data collections forms will be stored in locked rooms or, if available, in locked filing cabinets.

25.7 ELECTRONIC MAIL (E-MAIL) FILES

The Study Coordinator is primarily responsible for ensuring e-mail is printed and/or distributed as needed.

25.8 CONFERENCE CALLS AND STUDY SITE VISIT

Over the course of the study, the DCC will conduct site visits to each CCC and schedule conference calls with the principal investigators and coordinators to review recruitment and data quality. Site visits will be conducted for the purpose of observing operations, assessing adherence to protocols and certifying staff examination of procedures and interviews. Also, throughout the course of the study, each Clinical Center's performance will be monitored by a series of reports. These include reports of number of missing forms, rates of invalid data, rates of patients lost to follow-up and number of missed visits. These reports will routinely be sent to the Clinical Centers, the Steering Committee, CCCs, and the NIH Program Office.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 26: CONSENT FORM TEMPLATE AND AMENDMENT

26.1 CKiD CONSENT FORM TEMPLATE – 08/01/17

REMOVE ALL SHADED INSTRUCTIONS BEFORE PRINTING

**RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY
AUTHORIZATION FORM**

Protocol Title: Chronic Kidney Disease in Children Study (CKiD)

Sponsor: 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).

Principal Investigator:

1. What you should know about this study:

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please read it carefully and take as much time as you need.
- Ask questions about anything you do not understand now, or when you think of them later.
- You are a volunteer. If you do join the study and change your mind later, you may quit at any time without fear of penalty or loss of benefits.
- While you are in this study, the study team will keep you informed of any new information that could affect your decision to stay in the study.
- The word “you” in this consent form will refer to both you and your child unless specified.

2. Why is this research being done?

This research is being done to investigate what factors cause Chronic Kidney Disease (CKD) to become worse in children. CKD is when the kidneys have trouble removing waste products from the blood. The number of people with CKD continues to grow, and about 785,000 Americans will have ESRD by the year 2020. Since most people with CKD are adults, few studies have looked at CKD in children. Unfortunately, not all information from adult studies can be used to help children, since children develop CKD for different reasons than adults do.

In order to treat the problems caused by CKD in children, it is necessary to understand what causes CKD to get worse. The primary goals of this study are to determine what factors cause CKD to get worse in children, and to see how CKD affects a child’s brain development and behavior, heart function, growth and general well-being.

3. Who is doing this study?

Dr. *Insert PI's name* is in charge of the study. *Insert Coordinator's name* will coordinate the study. Other health care professionals may help them.

4. How many people will be in this study?

About 1080 children between the ages of 6 months and 16 years (before 17th birthday) at time of enrollment, with CKD, from about 50 different places around North America will be in this study. About *Insert Project Number* children will be asked to be in this study at *Insert Clinical Site Name*.

5. What will happen if you join this study?

Depending on when you enter the study, you may be in this study for up to 13 years (until July 31st, 2018). However, we plan to extend the study until July 31st, 2023. If you agree to be in this study or continue participating we will ask you to do the following things:

- **Receive pre-study material**

You will be given instructions prior to each study visit which may include a study brochure, a summary of study visits, scheduling information for the visits (dates, times, directions), and instructions on what to bring to the visit (for example, information that you may need to look up at home such as your child's birth weight), a copy of this signed consent form, and a copy of some of the forms for you to complete if you would like start them before the study visit.

- **Attend up to 16 study visits.**

NOTE: STUDY PROTOCOL LABELS STUDY VISITS AS: VISIT 1A, VISIT 1B, VISIT 2, VISIT 3, VISIT 4.....THROUGH VISIT 15. SOME IRBS MAY REQUIRE YOU TO LABEL STUDY VISITS ACCORDING TO THE NUMBER OF TIMES THE SUBJECTS COMES IN FOR VISIT: VISIT 1, VISIT 2, VISIT 3, VISIT 4, VISIT 5... FOR EXAMPLE, IF YOUR SITE ENROLLED A CHILD IN 2005, THEN THIS PARTICIPANT MAY COMPLETE UP TO 16 STUDY VISITS. HOWEVER, IF A CHILD ENROLLED IN 2006, THEN THE NUMBER OF POTENTIAL STUDY VISITS IS UP TO 15. REFER TO THE TABLE BELOW FOR FURTHER ILLUSTRATION. THIS TABLE DOES NOT NEED TO BE INCLUDED IN YOUR CONSENT FORM.

<i>Year of Enrollment (i.e. Completed Visit 1A)</i>	<i>Potential number of study visits completed by 2018</i>	<i>Potential visit number completed by 2018</i>
2005	16 (including irregular visit)	Visit 15
2006	15 (including irregular visit)	Visit 14
2007	14 (including irregular visit)	Visit 13
2008	13 (including irregular visit)	Visit 12
2009	12 (including irregular visit)	Visit 11
2010	11 (including irregular visit)	Visit 10
2011	10 (including irregular visit)	Visit 9
2012	9 (including irregular visit)	Visit 8
2013	8 (including irregular visit)	Visit 7
2014	7 (including irregular visit)	Visit 6
2016	3	Visit V2
2017	3	Visit V2
2018	2	Visit V1B

There will be one study visit per year except during the first year when there will be two study visits.

Study visits will take about 4 hours to complete. For children over the age of 3, Study Visit 1B will be within 6 months after Study Visit 1A. For children 6 months to 3 years of age, Study Visit 1B will occur within 3 months of the first visit. Study visits beginning with the V2 will take place annually after Study Visit 1A. All study visits will take place at *Insert location of visit*. During the study visits, we will collect information about your child's kidney function, brain development and behavior, heart function, and growth. We will also collect information from you such as family health history and your thoughts about your child's physical and emotional functioning.

If you will be unable to attend future study visits, or we notice during the study that your child's kidney function has become a lot worse, we will ask you to come back sooner for your next study visit. If you are unable to attend future study visits we would like to continue follow up with you on a yearly basis. This continued follow-up would be an interview that may be completed via phone, by mail, in-person interview or an on-line survey. As a part of this continued follow-up we will also look at your child's medical record for their most recent laboratory results, medical treatments, and measurements such as height, weight and blood pressure.

<<Only include the next paragraph if your site is participating in the Post RRT Pilot Study>>

If your child starts dialysis or receives a kidney transplant we would like to continue seeing you and your child for study visits. These visits are a little different than the visits described in this consent form so we will have you sign a separate consent form to continue in the study.

It is very important to go to all study visits for the information we gain to be most useful.

There is a chart of CKiD study visits attached to the end of this form.

- **Participate in the following study procedures:**

To study kidney function:

All children participating in the study will have blood and urine tests done (such as Creatinine) to measure kidney function at every visit except for the V1b. For children who are still in diapers, a urine sample may be collected using a urine bag, or by placing cotton balls in the diaper area.

In addition, some children may have an iohexol GFR (iGFR) test completed at Visits 1A, V2, V4, V6, V8, V10, V12 and V14. An iGFR test is a very accurate measurement of kidney function and level of CKD. This test measures Glomerular Filtration Rate (GFR). A visit with an iGFR test will last about 7 hours. If you joined the study before 2014, and your child's last iGFR measurement was 90 or higher, your child will be asked to complete the iohexol test. If you are joining the study after 2015, the iGFR test is optional and you can choose not to have the test done.

When the iGFR test is to be completed, your child will come to *Insert location of visit* in the morning. If you would like, we can apply a temporary numbing agent to the skin where needle sticks will occur. An IV catheter may be placed for drawing blood. A non-radioactive x-ray dye (Iohexol, brand name, Omnipaque®) will then be given through a small needle in a separate location from the IV because we need to give the Iohexol in a different place from the IV. Only about 1 teaspoon of Iohexol will be given over 1-2 minutes and then the small needle can be removed. Then we will take a small amount of blood (less than ¼ teaspoon) from the IV at 2 points in time after the Iohexol is given. The Iohexol test can also be done

using 3 separate needle-sticks instead of the IV if preferred. After the Iohexol is given, if drawing blood is difficult, finger sticks may be used to collect the blood samples. If we are unable to obtain the iGFR, you may be asked to reschedule the study visit.

To study brain development and behavior:

We will use some psychological surveys and tests to learn about your child's feelings, behaviors, and how they think and learn (cognitive abilities). Some of these instruments will be directly administered to your child by a trained professional at visits 1B, 3, 5 and 7. The testing time will vary depending on your child's age and ability but should not take more than 3 hours. The behavior questionnaires will be given to you to complete on your own starting at visit 1B and every two years after that. If the Neurocognitive testing cannot be completed during the scheduled study visit, it should be done within one month.

<<Only include the next paragraph if your site is participating in the NIH Toolbox Pilot Study>>

Participants who are 3 years old and older will complete some additional thinking exercises using an online program called the NIH Toolbox. The NIH Toolbox is a set of brief tasks used to assess how your child thinks and learns. These online exercises will be completed on an iPad at study visits 1B, 3, 5, and 7.

If your child is 8 years old or older they will also answer questions about their feelings. If your child is between 3 to 12 years old we will also ask you to complete questions about your child's feelings using the NIH Toolbox. These questions will be completed on an iPad starting at visit 1B and every other year after that.

To study heart function:

We will measure blood pressure during a physical at every study visit. We will use a special blood pressure machine that every child in this study will use. We will also take blood pressure the way you usually have it measured in clinic. We will also do blood tests that look at heart function at every visit.

Every two years beginning with V2, we will use an Ambulatory Blood Pressure Monitor (ABPM) to look for abnormal patterns of blood pressure over the day and night. The ABPM is a light-weight blood pressure cuff with a monitor worn on a belt or shoulder strap. A tube will connect the monitor to a blood pressure cuff on your child's arm. Your child will wear the ABPM for 24 hours. The ABPM will take blood pressure every 20 minutes during the day and night. We will give you instructions on how to return the ABPM to us.

Every four years beginning with the V2 an echocardiogram (ECHO) will be done. The ECHO uses sound waves (ultrasound) to take pictures of the heart. We use this to look for abnormalities of the heart.

<<Only include the next sentence if C-IMT testing is done at your site>> Also, for children who are 5 years of age and older, we will take a picture of the blood vessels that run through the neck (carotid arteries) using ultrasound in a test called Carotid Intima-Media Thickness (C-IMT).

<<Only include the next paragraph if Vascular testing is done at your site>> For children who are 5 years old and older, we will perform vascular tests every two years starting at V2. These tests will help us determine whether stiffer arteries put patients at risk for heart or kidney problems in the future. These tests do not use radiation (X-rays), ultrasound or needles; however, these tests give doctors information about the stiffness or flexibility of arteries. During this non-invasive procedure, your child will have sticky patches placed on their chest and a small instrument shaped like a pen will be placed on the wrist to record the heartbeat. This pen-shaped instrument has a highly-sensitive sensor on one end that can detect pressure

changes in the arteries. Then the same pen-shaped instrument will be placed on the side of your child's neck and the top of the leg to measure the speed of their pulse.

<<Only include next sentence if Heart Rate Variability is done at your site>>

Additionally, your child will lie still for 10 more minutes and their heart beat will be measured.

In children, eight (8) years old or older who meet the eligibility criteria, we will do a cardiac MRI of the heart. You will be asked to complete a questionnaire to ensure your child is eligible to have a cardiac MRI performed. This cardiac MRI is a safe, non-invasive test and it will be done once. The MRI uses radio waves, magnets and computers to take a picture of the heart. The picture will allow us to check for coronary heart disease and other conditions.

If the ECHO, <<Only include "Vascular Tests" if applicable to your site>> Vascular Tests, <<Only include "C-IMT" if applicable to your site>> C-IMT, Ambulatory Blood Pressure Monitoring (ABPM) or cardiac MRI cannot be obtained during the child's scheduled study visit, they should be completed within one month. If the ABPM cannot be obtained within a month of the visit, you may be asked to return to the clinic so that your child's manual blood pressure can be checked again so that it can be compared to the ABPM results.

<<Only include next paragraph if the Home BP Pilot Study will be done at your site>>

We may ask for you to collect blood pressure measurements on your child at home using a wireless blood pressure machine called the QardioArm. We will give you the machine and teach you how to use it during the study visit. At home you will be asked to collect blood pressure measurements for 3 days.

To study growth:

We will measure height, weight, waist and hip circumference during a physical exam at every study visit. If your child is less than 1 year old and/or unable to stand, we will collect the hip and waist measurement at your next visit.

If your child is less than 3 years old we will also measure head circumference at every study visit.

We will measure parental heights, if possible, during the first study visit.

We will do blood tests (such as calcium) that relate to growth at every study visit.

We will obtain dietary intake information each year.

If your child is 6 years old or older we will also measure your child's hand and forearm muscle strength. To do this, we will use a dynamometer to measure hand grip strength. This will be done starting at the V3 and every other year after that.

<<Only include next paragraph if the ActiGraph Pilot Study will be done at your site>>

We may measure your physical activity every year beginning with Visit 1B. To do this, we will ask you to wear a monitor continuously for 8 days. The monitor looks similar to a watch and will be worn on the wrist.

General study procedures:

Your child's doctor will give a brief physical exam at every study visit except for the second visit (Visit 1B).

- **Complete a variety of forms:**

We will ask you to complete several forms that ask for information about: you and your child's age, sex, race/ethnicity, education and household income; your child's medical history, your health literacy and numeracy, your child's birth and family history (birth weight, length, gestational age, complications during pregnancy, health of parents, grandparents, aunts, uncles, and siblings); what health care resources you use (for example, Medicare); any time your child spent in the hospital since the last study visit (and the reason); medications including herbal remedies, health supplements and/or vitamins, and over-the-counter drugs; dietary habits, sleep habits, physical activity of your child; and finally, environmental exposures (such as smoking and alcohol use for teens).

We may also collect information from your child's medical record. Information collected will include the following: diagnosis, lab results, mediations, hospitalizations, surgeries, and medical treatments. Tests related to kidney health and function (such as kidney ultrasounds or ambulatory blood pressure monitoring reports) may be reviewed by a researcher selected by the CKiD study. This may be a physician outside of *Insert Clinical Site Name*.

- **Receive test results**

You will receive the results of the Iohexol GFR test (if completed), notification of any critical blood or urine laboratory values, and notification of any new abnormalities found with the ABPM or ultrasound tests. You will be informed, through your nephrologist, if your answers on the behavioral questionnaires suggest the possibility that your child is at risk for self-injury or injury to others. You will also receive a feedback report summarizing the results of the psychological testing. *<<Only include next sentence if the ActiGraph Pilot Study will be done at your site>>* In addition, you will also be given a summary of your activity level if you wear the physical activity monitor. If you want, the results of your child's tests will be given to your other doctors.

- **Donate OPTIONAL biological and genetic samples.**

OPTIONAL Biological Sample:

We would like to draw a small amount of blood (about 2-3 teaspoons depending on your child's weight) at each study visit beginning with the V1B that will be sent to the NIDDK Central Repository, which is a research resource supported by the National Institutes of Health (NIH). Additionally, we would like to send urine samples to the Repository from each study visit beginning with the V1B. We would also like to send a sample of your child's fingernail/toenail clippings and a sample of your child's hair (about 20 fibers) from Study Visit 1B to the same Repository. If the nail clippings and hair samples are not collected at V1B, then the sample will be collected and shipped at the next study visit. At visit 4, we would also like to send an additional sample of your child's toenail clippings to the same Repository. If the toenail clippings are not obtained at visit 4, they will be collected and shipped at your next study visit. The Repository collects, stores, and distributes biological samples and associated data from people with many kinds of disorders, from healthy family members, and from other healthy people. The purpose of this collection is to provide available samples for future research of CKD. Sending samples to the Repository may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments and new ways to prevent disease. If all 16 study visits are completed, the amount of extra blood will be about 28 to 47 teaspoons over the entire study depending upon your child's weight. The total amount of blood for Study Visit 1B through 15 including the Biological Sample will be approximately 3 to 6 teaspoons per visit depending on your child's weight and if your child will have an iohexol GFR completed.

Before your child's sample is sent to the Repository, the sample will be given a code number that will not include your child's name or other personal identifying information, such as address, social security number, and date of birth. Therefore, the Repository will not be able to give out your child's name, or other information that identifies your child, to the scientists who receive the samples.

You can choose not to participate in this portion of the study and still participate in the rest of the study. If you agree to have your child's sample stored in the Repository, you can change your mind up until the end of the CKiD study. When study researchers receive written instructions from you, they will destroy your child's sample. After the CKiD study ends, you will not be able to withdraw your child's sample because the Repository will not know which one is your child's. The sample will stay in the Repository indefinitely.

- I DO WISH FOR MY CHILD TO PARTICIPATE IN THE BIOLOGICAL SAMPLE PART OF THIS STUDY**

Initials

Date

- I DO NOT WISH FOR MY CHILD TO PARTICIPATE IN THE BIOLOGICAL SAMPLE PART OF THIS STUDY**

Initials

Date

OPTIONAL Genetic Sample:

We would also like to draw another small amount of blood that will be sent to the Rutgers Genetic Repository in New Brunswick, NJ. We would like to obtain this sample at Study Visit 1B. The amount of extra blood will be about 2 teaspoons. 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. The total amount of blood for Study Visit 1B including the Biological and Genetic Sample will be about 3 to 4 teaspoons depending on your child's weight. The same standards and guidelines for the Biological Samples apply to the Genetic Samples.

If you choose to participate in this optional part of the study, genetic testing will be done on your child's blood sample. Genetic testing looks at pieces of DNA called genes, which contain the information needed to build and operate the human body. Scientists will look at DNA of the blood to help them develop new diagnostic tests, new treatments and new ways to prevent disease. Your child's sample will be stored in a way that allows cells to grow and multiply. These multiplying cells may give rise to what is called a cell line. Cell lines may be kept alive indefinitely or for many years and can be used for many different studies in the future. Some future studies may include looking at a complete set of DNA to look for variations in genes. These samples and test results may be shared with other researchers and scientists. However, they will not know who your child is as they will only receive the sample with a coded number without any personal identifying information. It will not be possible to share any test results with you or your doctors because the samples and test results will be coded.

- I DO WISH FOR MY CHILD TO PARTICIPATE IN THE GENETIC SAMPLE PART OF THIS STUDY**

Initials

Date

I DO NOT WISH FOR MY CHILD TO PARTICIPATE IN THE GENETIC SAMPLE PART OF THIS STUDY

Initials

Date

• **OPTIONAL sharing of information for ongoing research**

Consent for Use of Data for Future Research

To further help us understand what happens to people who have CKD for many years, we may want to obtain information about your child's health status in the future. Public health databases supported by the government (*such as the Census, Unites States Renal Data System [USRDS], Scientific Registry of Transplant Recipients [SRTR], <<CANADIAN SITES SHOULD LIST the Canadian Organ Replacement Register [CORR] instead of the Census, USRDS, or SRTR>>*) may provide the CKiD study with valuable information in the years to come about your child's health and medical treatments such as dialysis and transplant.

National databases collect and file information by social security number, <<CANADIAN SITES SHOULD LIST THE PROVINCIAL HEALTH ID INSTEAD OF SSN>> name, date of birth, and gender. With your permission, the CKiD study would like to periodically check if there is health related information on file about your child in a public health database by using your child's personal identifiers to request health information.

<<The following description of the Honest Broker only pertains to CKiD study sites in the United States>>>

In order to protect your child's identity, a third party called an Honest Broker will be used. By using the Honest Broker, the CKiD study will not receive any of your child's personal identifiers. The Children's Hospital of Philadelphia Research Institute will be the Honest Broker for this study.

With your permission,

- *Insert Clinical Site Name* will provide the Honest Broker with a CKiD study identification number along with your child's social security number, name, date of birth, and gender.
- The Honest Broker will provide the personal identifiers to the databases along with a coded number that is different from the CKiD study identification number.
- The databases will provide health information to the Honest Broker with only the coded number attached.
- The Honest Broker will replace the coded number with the CKiD identification number and send the health information to the CKiD study's Data Coordinating Center. There are no public records that could link the CKiD study identification number to your child's personal information.

This process will keep your child's social security number and name separate from any medical study information that the CKiD study has on record.

Your child's information will only be available to researchers who are specifically approved to do these studies. Because we want to look at your kidney health over a long period of time, your permission to use your personal identifiers has no time limit. We will continue to check for information even if you are no longer taking part in the study. You can change your mind about participating in this optional part of the study at any time. If at a later date you decide you no longer want to participate you must inform the study doctor or study team that you would like to cancel your permission to use your personal identifiers to

request your health information from public health databases. Information that has already been collected will be kept, however, no further information about your child will be collected. You can still participate in the rest of this study even if you do not want to participate in this portion. Please indicate whether you are willing to allow the researchers to use your child's personal information for this future research by marking YES or NO and providing your initials and the date below:

MY CHILD'S SOCIAL SECURITY NUMBER, , <<CANADIAN SITES SHOULD LIST THE PROVINCIAL HEALTH ID INSTEAD OF SSN>>NAME, DATE OF BIRTH, AND GENDER MAY BE USED TO LINK PUBLIC HEALTH DATABASE INFORMATION FOR USE IN THE CKiD STUDY.

YES NO Initials _____ Date _____

Consent for Sharing of Data Between Research Studies

If you enroll in another research study at *Insert Clinical Site Name*, some procedures and questionnaires may be done in both studies. This may include lab test results, medical history or other information about you/your child such as age, race, education, and household income. In this case, information collected in one study may be shared with the other, so you will not have to repeat it again. This information will only be shared if you agree to participate in both studies. You can change your mind about participating in this optional part of the study at any time. Please indicate whether you are willing to allow the researchers to share your child's information at *Insert Clinical Site Name* by marking YES or NO and providing your initials and the date.

INFORMATION OBTAINED BY THE CKiD STUDY MAY BE SHARED WITH ANOTHER STUDY PERFORMED AT *Insert Clinical Site Name*.

YES NO Initials _____ Date _____

- **OPTIONAL Consent for the iGFR Test (Only for study participants joining the study after 2015)**
If you join the study after 2015 you can choose whether or not to have an iohexol GFR test performed at Visits 1A, V2, V4, V6, V8, V10, V12 and V14. The test is described in detail on page 3 of this consent form. You can change your mind about participating in this optional part of the study at any time. You can still participate in the rest of this study even if you do not want to participate in this portion. Please indicate whether you are willing to have iGFR testing by marking YES, or NO.

I AGREE TO HAVE THE IOHEOXL TEST DONE AS A PART OF THE STUDY

YES NO Initials _____ Date _____

6. What are the risks or discomforts of the study?

There are certain risks in this study. These risks may include:

Urine Collection Bag

If your child is still in diapers a urine bag may be used to collect a urine sample. Skin redness or irritation may result from the collection bag but it is rare.

iGFR Test

Iohexol (Omnipaque®) is a non-toxic dye regularly used in Radiology for special x-ray studies of the abdomen and chest like CT scans. While the dose in Radiology is generally 50-200 cc, we will use 5 cc (1 teaspoon) for the GFR procedure. In a study of about 500 children in Scandinavia given Iohexol to get GFR using the same small dose specified in our study, Iohexol did not cause side effects. In a review of over 8000 GFR determinations, the authors report no complications except for 2 patients who experienced transient malaise and vomiting between 1 and 3 hours after injection of the Iohexol. It was uncertain whether this was indeed caused by the Iohexol.

At 20 times the dose to be given in this study, Iohexol has caused heart rhythm problems in less than 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, changes in blood pressure, changes in heart rate, dizziness and fainting. Iohexol would not be used if a patient had a previous history of difficulty breathing after IV injection 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 injection. We will watch the blood pressure and pulse after the Iohexol injection.

Blood Draws and Insertion of an Intravenous Catheters:

Drawing blood or inserting an IV catheter may cause some pain, bleeding or bruising at the spot where the needle enters or where the plastic tube stays in your body. Rarely, the procedure can cause fainting or infection or swelling of the vein. Sometimes, the tip of the catheter or needle could withdraw from the vein or poke through the vein causing the Iohexol to leak (infiltrate) into the surrounding tissue. This may cause some pain or swelling but there is very little risk of tissue damage. If the Iohexol infiltrates, the GFR test cannot be performed we will ask you to reschedule the test for another day. Your child's doctors and nurses will be checking often to see if any side effects are occurring.

ABPM <<Only include "home blood pressure monitor" if the Home BP Pilot study will be done at your site>> or home blood pressure monitor

Possible risks associated with use of the ABPM <<Only include "home blood pressure monitor" if the Home BP Pilot study will be done at your site>> or home blood pressure monitor include discomfort, bruising, or injury to the arm when the blood pressure cuff is inflated.

Echocardiogram <<Only include "C-IMT" if this testing is done at your site>> and C-IMT:
There are no confirmed side effects from present diagnostic ultrasound instruments (echocardiogram <<Only include "C-IMT" if this testing is done at your site>> and C-IMT).

<<Only include next paragraph if Vascular testing is done at your site>>

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.

Cardiac MRI

There are no known side effects with a cardiac MRI. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. Because MRI uses powerful magnets, the presence of metal in your body may be a safety hazard. Prior to the exam, you will be asked to complete a standard questionnaire. The purpose of this questionnaire is to ensure that it is safe to enter the MRI area. The questionnaire and the way the MRI staff position you on the table are very important to ensure your child will be safe during the MRI.

Neurocognitive Tests <<Only include next phrase if your site is participating in the NIH Toolbox Pilot study>> or NIH Toolbox assessment

Some questions may make you feel upset or uncomfortable. You do not have to answer any questions that make you or your child feel upset or uncomfortable. If you have any of these problems, you should tell the investigator or other study personnel as soon as possible.

Grip Strength

There are no confirmed side effects from using the grip strength instrument.

Physical Activity Monitor

There are no confirmed side effects from using the ActiGraph monitor to measure activity.

Confidentiality

As with all studies in which data is collected from the participant, there is also a risk for the loss of confidentiality of sensitive information.

7. Are there risks related to pregnancy?

Your child should not be in this study if she is pregnant or breast feeding. If you think your child may have become pregnant, please tell the study investigator or other study personnel. If your child is a girl and old enough to get pregnant, a urine pregnancy test will be performed annually. If the urine test indicates pregnancy, your child will be ineligible to continue with the main study, but could participate in the continued (PIP) follow-up interviews or on-line surveys.

8. Are there benefits to being in the study?

There is no direct benefit to your child from being in this study. Possible benefits may include:

- Having a GFR measurement can benefit your child's clinical care. A better measure of GFR will allow a better assessment of risk for kidney disease progression, as well as safer dosing of drugs that can cause kidney damage and other drugs that are cleared by the kidney. We will also be able to start better blood pressure control and low-protein diets at earlier stages of CKD.
- Many of the tests for brain development and behavior, heart function, and growth would not be done as part of your child's routine care. Therefore, you will have more specific information about your child's health.
- By being in this study, you may help children with CKD in the future.

9. What are your options if you do not want to be in the study?

Instead of participating in this study, you may choose not to enter this study. You do not have to join this study. If you do not join, your care at *Insert Clinical Site Name* will not be affected.

10. Will it cost you anything to be in this study?

The study procedures will be provided at no cost to you.

8. Will you be paid if you join this study?

<<PLEASE CHECK \$ AMOUNTS FOR YOUR CLINICAL SITE>>

To help you pay for the costs involved with this study (missing work, transportation, meals, sibling care, time to complete the numerous forms and tests, watching the ABPM and sending it back to us, etc.) you will receive the following:

- \$100 for each study visit completed (Visit 1A through V14)
- An additional \$50 for completion of an iohexol test at Study Visit (1A, V2, V4, V6, V8... etc.)
- An additional \$50 for completion of a cardiac MRI
- **<<Only include if the ActiGraph Pilot Study will be done at your site>>** An additional \$10 for completion of the physical activity monitor
- If you need to return to the clinic on a second day to complete an ECHO, ABPM, or cognitive test, you will receive an additional \$25.
- A small gift, such as a gift certificate, may be given to your child at each study visit. Holiday cards, birthday cards or thank you cards may be given to the families as a token of appreciation for their participation.
- \$50 for each continued follow-up (PIP) interview, or on-line survey completed.

9. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

10. Why might we take you out of the study early?

You may be taken out of the study if:

- Staying in the study would be harmful.
- Your child needs treatment not allowed in this study.
- You fail to follow instructions.
- Your child becomes pregnant. Your child would not be allowed to continue with study visits, but can participate in the continued follow-up interviews or online survey.
- There may be other reasons to take your child out of the study that we do not know at this time.

11. How will your privacy be protected?

Insert Clinical Site Name has rules to protect information about you. Federal and state laws also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

Generally, only people on the research team will know that you are in the research study and will see your information. However, there are a few exceptions that are listed later in this section of the consent form.

Unless you give permission or the board that reviews research studies approves it, no one else will be able to see or use your information.

The people working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may collect other information including your name, address, date of birth, social security number and other details.

The research team will need to see your information. Sometimes other people at *Insert Clinical Site Name* may see or give out your information. These include people who review the research studies, their staff, lawyers, or other *Insert Clinical Site Name* staff.

People outside of *Insert Clinical Site Name* may need to see your information for this study. Examples include government groups, safety monitors, and other hospitals in the study and companies that sponsor the study.

If you gave permission on page *Insert page number*, the Honest Broker located at Children’s Hospital of Philadelphia, and public health databases such as the Census, United States Renal Data System, and the Scientific Registry of Transplant Recipients may receive your personal information.

We cannot do this study without your permission to use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will use and disclose your information only for the purposes stated in the study. The use of your information has no time limit. You can cancel your permission to use and disclose your information at any time by calling the *Insert Clinical Site Name* IRB at *Insert phone number of clinical center IRB* or by sending a letter to:

<<*INSERT MAILING ADDRESS OF CLINICAL CENTER IRB*>>

Your cancellation would not affect information already collected in this study.

We try to make sure that everyone who needs to see your information uses it only for the study and keeps it confidential – but we cannot guarantee this.

12. What if there is a Certificate of Confidentiality for this study?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, 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 you, 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 you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your 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 self or others that is disclosed by you or your child.

13. What other things should you know about this research study?

- **What is the Institutional Review Board (IRB) and how does it protect you?**

The *Insert Clinical Site Name* IRB is made up of doctors, nurses, ethicists, non-scientists, and people from the local community. The IRB's purpose is to review human research studies and to protect the rights and welfare of the people participating in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is *Insert phone number of clinical center IRB*.

- **What do you do if you have questions about the study?**

Call the principal investigator, *Insert PI Name* at *Inset PI's phone number*.

- **What should you do if you are injured or ill as a result of being this study?**

If you have an urgent medical problem related to your participation in this study, call *Insert PI Name* or the Pediatric Nephrology Fellow on call at *Insert emergency phone contact number* <<IF THIS IS A PAGER #, INSERT: >> "After the tone, enter the phone number where you can be called, press the # key, and hang up."

If you think you are injured or ill as a result of being in this study, call the principal investigator, *Insert PI Name* at *Inset PI's phone number*.

The medical services at *Insert Clinical Site Name* will be open to you as they are to all sick or injured individuals. *Insert Clinical Site Name* does not have a program to pay you if you are hurt or have other bad results from being in the study. You are financially responsible for payment of any treatment or hospitalization. At your request, your insurance provider will be billed for payment of any treatment or hospitalization.

- **What happens to Data, Tissue, Blood and Samples that are collected in the study?**

Insert Clinical Site Name is dedicated to finding the causes and cures of disease. The data, tissue, blood and samples from your body collected during this study are important to this study and to future research. If you join this study,

- You will not own the data, or tissue, blood or other specimens given by you to the investigators for this research.
- Both *Insert Clinical Site Name* and any sponsor of the research may study your data and the tissue, blood or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, *Insert Clinical Site Name* may use them for future research only with your consent or IRB approval.
- You will not own any product or idea created by the researchers working on this study.
- You will not receive any financial benefit from the creation, use or sale of such a product or idea.

<<Only add the following section (e) if other organizations need to be listed>>

- **What are the Organizations that are part of <<NAME OF CLINICAL INSTITUTION>>?**

<<IF APPLICABLE, LIST THE DIFFERENT HEALTH CARE PROVIDERS ASSOCIATED WITH YOUR INSTITUTION>>

17. Assent Statement

This research study has been explained to my child in my presence in language my child can understand. He/she has been encouraged to ask questions about the study now and at any time in the future.

18. What does your signature on this consent form mean?

By signing this consent form, you are not giving up any legal rights. Your signature means that you understand the information given to you in this form, you accept the provisions in the form, and you agree to join the study.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

Signature of Participant Date

Signature of Person Obtaining Consent Date

Add any of the following that are applicable for this study and delete any that do not apply

Signature of Legally Authorized Representative (LAR) for **ADULTS NOT CAPABLE of GIVING CONSENT** Date
(Persons from the following categories in order of priority may be a Legally Authorized Representative: Health Care Agent; Legal Guardian; Spouse; Adult child; Parent; Adult sibling; Friend or other relative)

Relationship of LAR to Participant (indicate why the LAR is authorized to act as a surrogate health care decision-maker) Date

Signature of Parent/Guardian Date

Signature of Parent #2 (required if DHHS 45 CFR 46.406 or 46.407/FDA 21 CFR 50.53 or 50.54 study) Date

Signature of Child Participant (optional unless IRB required) Date

Signature of Witness to Consent Procedures (optional unless IRB or Sponsor required) Date

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; AND, IF APPROPRIATE A COPY OF THE CONSENT FORM MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD.

CKiD STUDY TIMETABLE

Name of Visit	Pre-Study	V1A	V1B	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V2	V13	V14
Timing of Visit		First visit	3-6 months after V1A	1 year after V1A	2 years after V1A	3 years after V1A	4 years after V1A	5 years after V1A	6 years after V1A	7 years after V1A	8 years after V1A	9 years after V1A	10 years after V1A	11 years after V1A	12 years after V1A	13 years after V1A
Approximate Length of Visit	45mins	All study visits will take approximately 4 – 5 hours. If your child is having the iohexol GFR test the study visit will take 7 hours														
Consent	X															
Family Information	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam, Blood and urine samples		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (if applicable)		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Questionnaires and Forms (optional to start before the first visit)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ABPM				X		X		X		X		X		X		X
Echo and C-IMT				X				X				X				X
Vascular Tests				X		X		X		X		X		X		X
Home Blood Pressure Monitoring				X	X	X	X	X	X	X	X	X	X	X	X	X
Learning Ability Tests			X		X		X		X							
NIH Toolbox Tests (iPad)																
Behavior Questionnaires			X		X		X		X		X		X		X	
Grip Strength					X		X		X		X		X		X	
Physical Activity Monitor			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiac MRI			X													
iGFR Test Optional for those enrolled after 2015. Done if iGFR is ≥ 90 for those enrolled before 2015		X		X		X		X		X		X		X		X
OPTIONAL – Biological blood and urine samples			X	X	X	X	X	X	X	X	X	X	X	X	X	X
OPTIONAL – Biological hair and nail samples			X													
OPTIONAL – Genetic sample			X													
OPTIONAL – Biological Toenail Samples						X										

26.2 CONSENT FORM AMENDMENT 1:

26.2.1 EAST COAST CONSENT FORM AMENDMENT 1:

CKiD Consent Form Table-lists the changes from 10/07/04 version of the Consent Form Template to 04/01/05

* All changes to original text will be printed in *italics* *

Page #(s) on Original Consent Form Template (found on the CKiD CD)	Change to Consent Form	Required or Recommended Changes
1	In the section under “Why is this research being done”: 1) CHANGE: Children <i>between the ages of 1 and 16 years (before 17th birthday)</i> with mild to moderate CKD may join this study.	Required
1	In the section under “Attend up to five study visits”: 1) CHANGE: About 540 children will be in this study at <i>57</i> different places...	Recommended
1	ADD the following section under “What will happen if you join this study?”: <i>A) Receive pre-study material You and your child will be given a Family Binder before each study visit which may include items such as a study brochure, an outline of study visits, scheduling information for the visits (dates, times, directions), instructions on what to bring to the visit (for example, information you may need to look up at home such as your child’s birth weight), a copy of this signed consent form, and a copy of some of the forms for you and your child to complete if you would like to start them before the study visit.”</i> NOTE: Adding this section will change the letter headings that follow.	Recommended
1	In the section under “Attend up to five study visits”: 2) CHANGE the names of the study visits from 1, 2, 3, 4 and 5 to <i>1A, 1B, 2, 3 and 4</i> 3) ADD the following sentence: <i>For children over the age of 3, Study Visit 1B will be between 3 and 6 months after Study Visit 1A. For children 1 to 3 years of age, the second study visit will be within 3 months of the first visit. Study visits 2, 3, and 4 will take place annually after Study Visit 1B.</i> 4) ADD the following sentence: <i>All study visits will take place at <<ENTER LOCATION>>.</i>	1) Required 2) Recommended 3) Recommended
2	In the section under “To study kidney function”: 1) DELETE the following sentences: <i>Your child will be asked to eat a low-protein diet 24 hours before the GFR. Low-protein diet instructions will be provided.</i> ADD the following sentence: <i>Upon request we can apply EMLA or LMX 4 (Elam ax) cream to numb the IV sites.</i>	Required Recommended

	<p>2) CHANGE: Then we will take a small amount of blood (less than ¼ teaspoon) at 4 points in time after the Iohexol is given.</p>	<p>Required</p>
<p>2</p>	<p>In the section under “To study brain development and behavior”:</p> <p>1) DELETE ALL listings and details of specific tests to be used and ADD the following two sections (WE STRONGLY RECOMMEND THIS CHANGE IF YOUR IRB WILL ALLOW IT):</p> <p><i>i. We will use some psychological surveys and tests to learn about your child’s thoughts, feelings, behaviors and cognitive abilities. Some of these instruments will be directly administered to your child by a trained professional and some of these instruments will be given to you to complete on your own. The testing time will vary depending on your child’s age and ability but should not take more than 3 hours. You will receive written feedback about your child’s performance on the cognitive tests. Your nephrologist will also receive a copy of this feedback. You will also be informed, through your nephrologist, if your child’s answers suggest the possibility of self-injury or injury to others.</i></p> <p><i>ii. <<ONLY LEAVE THIS BULLET IN THE CONSENT FORM IF YOUR SITE IS THE UNIVERSITY OF NORTH CAROLINA OR MONTEFIORE MEDICAL CENTER>></i> <i>We will ask some children who are considered “high risk” for neurocognitive impairment to undergo about one hour of additional testing depending on his/her age. These additional instruments will look at different types of memory, problem-solving, verbal and nonverbal efficiency, visual and spatial skills, and language abilities.</i></p> <p>2) IF YOU MUST LIST ALL SPECIFIC NEUROCOG TESTS, DELETE THE FOLLOWING TESTS IF YOUR CENTER IS NOT THE UNIVERISTY OF NORTH CAROLINA OR MONTEFIORE:</p> <p>a. Children’s Memory Scale (CMS) b. Delis-Kaplan Executive Function System (D-KEFS) c. Benton Judgment of Line Orientation and Form Discrimination (Benton) d. Clinical Evaluation of Language Fundamentals – 4th Edition (CELF-4)</p> <p>3) IF YOU MUST LIST ALL SPECIFIC NEUROCOG TESTS, ADD THE FOLLOWING TESTS:</p> <p><i>a. Children’s Depression Inventory (CDI) – will be administered to children aged 7 to 18 years old.. It is designed to assess depression symptoms in children.</i></p> <p><i>b. Behavior Rating Inventory for Executive Functions – Preschool Version (BRIEF-P) – will be completed by parents of children aged 2 to 6 years. This form assesses the child’s executive functions within the context of home and preschool environments.</i></p> <p><i>c. Behavior Rating Inventory for Executive Functions (BRIEF) – Parents of children aged 6 to 18 years will complete this form. This form assesses executive function behaviors (i.e. inability to initiate and carry-out new and goal-directed patterns of behavior).</i></p> <p><i>d. Wechsler Individual Achievement Test Second Ed.-Abbreviated (WIAT-II-A) – Administered to all children aged 6 years and older. The WIAT-II-A comprises three key subtests that best represent the core domains of reading, writing, and arithmetic.</i></p>	<p>Recommended</p> <p>1) Required</p> <p>2) Required</p>

	<p>3) IF YOU MUST LIST ALL SPECIFIC NEUROCOG TESTS, <u>DELETE</u> THE NAMES AND DESCRIPTIONS OF THE FOLLOWING TESTS:</p> <p>a. <i>Alpern-Boll Developmental Profile II (ABDP II)</i> b. <i>Visual Analog Scale (VAS)</i> c. <i>Child Behavior Checklist (CBCL)</i></p> <p>4) IF YOU MUST LIST ALL SPECIFIC NEUROCOG TESTS, <u>MAKE THE FOLLOWING CHANGES FOR THE FOLLOWING TESTS:</u></p> <p>a. Mullen Scales of Early Learning (for 12-29 month old children)</p> <p>b. Behavior Assessment System for Children – <i>Second Edition (BASC-2)</i></p> <ul style="list-style-type: none"> • <i>BASC-2 Parental Rating Scales</i> – for parents of children 2 to 18 years old • <i>BASC-2 Self Report of Personality</i> – for children 8 to 18 years old <p>c. Wechsler Abbreviated Scales of Intelligence (for 6 to 18 year old children)</p> <p>d. Pediatrics Quality of Life – administered to children 8 years and older, and to parents of children aged 2-16 years</p> <p>e. Connors’ Continuous Performance Test II – for children 6 to 18 years old</p>	<p>3) Required</p> <p>4) Required</p>
3	<p>In the section under “To study heart function”:</p> <p>1) ADD the following sentence: <i>The ABPM will be worn for Study Visits 2 and 4.</i></p> <p>2) DELETE the following sentence: <i>The special blood pressure machine will take your child’s blood pressure 4 times (every 2 minutes) so that we can get a very good measurement.</i></p> <p>3) IF APPLICABLE, ADD the following sentence: <i>In some children, we will also take a picture with ultrasound of the carotid arteries (blood vessels that run through the neck)</i></p>	<p>1) Recommended</p> <p>2) Recommended</p> <p>3) Required</p>
3	<p>In the section under “To study growth”:</p> <p>1) ADD the following sentence: <i>For this three-day diet record, you will have the option of obtaining data from your child’s school (type of lunch, nutrition information, etc.) to help make this diet history more complete.</i></p>	<p>1) Recommended</p>
3	<p>In the section under “Complete a variety of forms:”</p> <p>1) DELETE “for the previous day” in the clause regarding physical activity</p>	<p>1) Recommended</p>
3	<p>ADD the following section after the section entitled “Complete a variety of forms”:</p> <p><i>E) You will receive the results of the Iohexol GFR test, notification of any critical blood or urine laboratory values, and notification of any new abnormalities found with the ABPM or ultrasound tests. You will also receive a feedback report summarizing the results of the psychological testing. If you want, the results of your tests will be given to your other doctors.</i></p>	<p>Recommended</p>

3, 4	<p>In the section under “OPTIONAL Biological Sample”:</p> <ol style="list-style-type: none"> 1) CHANGE first sentence to: We would like to draw a small amount of blood (<i>about 1-2 teaspoons depending on your child’s weight</i>) at Visits 1B, 2, 3, and 4 that will be sent to the NIDDK Central Repository, 2) ADD the following sentence after the first sentence: <i>Additionally, we would like to send urine samples to the Repository from Visits 1B, 2, 3 and 4.</i> 3) CHANGE the following sentence: We would also like to send a sample of your child’s fingernail/<i>toenail</i> clippings and a sample of your child’s hair (<i>about 20 fibers</i>) from Study Visit 1B to the same Repository. 4) CHANGE the following sentence: The amount of extra blood will be about 4 to 8 teaspoons over the entire study depending upon your child’s weight. The total amount of blood for Study Visit 1B, 2, 3 and 4 including the Biological Sample will be approximately 3 to 6 teaspoons depending on your child’s weight. 5) DELETE the following sentences: <ol style="list-style-type: none"> a. <i>The Repository will take measures to protect your child’s privacy, although no guarantee of confidentiality can be absolute.</i> b. <i>However, the Repository will have some data about your child such as age, sex, race, and diagnosis.</i> 	<p>i. Required</p> <p>i. Required</p> <p>i. Required</p> <p>y. Required</p> <p>y. Required</p>
4	<p>In the section under “OPTIONAL Genetic Sample”:</p> <ol style="list-style-type: none"> 1) CHANGE “NIDDK Genetic Repository” to “Rutgers Genetic Repository” 2) CHANGE the following sentence: We would like to obtain this sample at Study Visit 1B. 3) CHANGE the following sentences: The amount of extra blood will be about 2 teaspoons. The total amount of blood for Study Visit 1B including the Biological and Genetic Sample will be about 3 to 4 tablespoons depending on your child’s weight. 	<p>1) Required</p> <p>2) Required</p> <p>3) Required</p>
5, 6	<p>DELETE the sections describing “Pre-Study,” “Study Visit 1,” “Study Visit 2,” “Study Visit 3,” “Study Visit 4,” and “Study Visit 5.” This information is listed elsewhere in the consent form.</p>	<p>Recommended</p>
7	<p>In the section related to Risks or Discomforts of the study:</p> <ol style="list-style-type: none"> 1) ADD <u>Confidentiality</u>: <i>As with all studies in which data is collected from the participant, there is also a risk for the loss of confidentiality of sensitive information.</i> 	<p>1) Recommended</p>
7	<p>In the section entitled “Are there risks related to pregnancy?”:</p> <ol style="list-style-type: none"> 1) DELETE “<i>or fathered a child</i>” 2) ADD: <i>If your child is a girl and old enough to get pregnant, a urine pregnancy test will be performed annually. If the urine test indicates pregnancy, your child would be ineligible to continue with the study.</i> 	<p>1) Required</p> <p>2) Required</p>
7	<p>In the section entitled “Will you be paid if you join this study?”:</p> <ol style="list-style-type: none"> 1) CHANGE the names of the study visits from 1, 2, 3, 4 and 5 to 1A, 1B, 2, 3 and 4 2) CHANGE the amounts of the honorarium for each visit if they are different than those listed (\$150, \$75, etc.) 3) CHANGE the following sentence: A small gift, such as a gift certificate, will be given to your child at each visit. 4) DELETE the following sentences: <i>If the total value of compensation to you or your child for being in research studies at <<CLINICAL CENTER NAME>> totals more than \$600 in any calendar year, the hospital must report this to the IRS on a Form 1099 with the recipient’s social security number. You will receive a copy of this form.</i> 	<p>1) Required</p> <p>2) Required</p> <p>3) Recommended</p> <p>4) Recommended</p>
9	<p>ADD the following section before the section entitled “What other things should you know about this research study?”:</p> <p><u>What if there is a Certificate of Confidentiality for this study?</u></p> <p><i>To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal,</i></p>	<p>Required</p>

	<p><i>administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.</i></p> <p><i>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).</i></p> <p><i>The Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.</i></p> <p><i>The Certificate of Confidentiality does not prevent the researchers from disclosing information about intent to hurt self or others that is disclosed by you or your child.</i></p>	
10	<p>ADD the following section before the section entitled “What does your signature on this consent form mean?”</p> <p><u>Assent Statement</u> <i>This research study has been explained to my child in my presence in language my child can understand. He/she has been encouraged to ask questions about the study now and at any time in the future.</i></p>	Recommended
12	<p>AMEND the CKiD Study Timetable:</p> <ol style="list-style-type: none"> 1) Column Heading should read: <i>Pre-Study; Study Visit 1A (year 1); Study Visit 1B (1-6 months after Visit 1A); Study Visit 2 (~1 year after Visit 1A); Study Visit 3 (~1 year after Visit 2); Study Visit 4 (~1 year after Visit 3)</i> 2) Change “Participant Binder” to “Family Binder;” X’s should be in all boxes except under V1A 3) There should be 2 rows for optional biological samples <ol style="list-style-type: none"> b. OPTIONAL- Biological blood and urine samples: X’s at V1B, V2, V3, V4 c. OPTIONAL- Biological hair and nail samples: X at 1B 	<p>i. Required</p> <p>i. Required</p> <p>i. Required</p>

26.2.2 MIDWEST CLINICAL SITES - CONSENT FORM AMENDMENT 1:

CKiD Consent Form Table-lists the changes from 10/07/04 version of the Consent Form Template to 04/01/05

Page #(s) on Updated Protocol	CHANGE(S)	Rationale (if applicable)	Consent form Changes
9-11	Changed 54 sites to 57 sites; Principal Investigator names and sites added to table	Suggestion to update the clinical sites and PI's that are involved in the CKiD study	"About 540 children will be in the study at 57 different places..."
9	Additional funding is provided by the National Institute of Neurological Disorders and Stroke, the National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute	Suggestion to further clarify national funding resources	Consent form template provided to you on CD included these sponsors; although protocol did not
12	<p>1. Highly sensitive C reactive protein has been updated to wide range C reactive protein throughout the protocol</p> <p>2. Participants will be given the option to contribute samples beginning at study visit 1b.</p> <p>3. Blood and urine specimens will be collected at baseline and at each annual follow-up visit.</p> <p>4. Nail clippings and hair samples will be collected at baseline.</p> <p>5. Also deleted: "Each repository has obtained a Certificate of Confidentiality from the Federal Government to assure privacy."</p>	<p>1. Suggestion to clarify the reporting of lab results.</p> <p>2. Suggestion to update the terminology for C reactive protein.</p> <p>3, 4, 5 Suggestion to modify and clarify the optional biological and genetic specimens to be collected for storage at the repositories and the schedule of collecting these specimens.</p> <p>6. We plan to obtain a Certificate of Confidentiality for the entire study. See rationale page 86-87.</p>	<p>1. No change needed to consent</p> <p>2. No change needed to consent</p> <p>3,4,5. Change wording in the table to Optional-Biological blood and urine samples to Visits 2(1b),3,4,&5. Add a row titled Optional- Biological hair and nail samples and place the X at Visit 2 (1b). Change visit numbers under OPTIONAL Biological Sample:</p> <p>"We would like to draw a small amount of blood at Visits 2 (1b), 3, 4 and 5 that will be sent to the NIDDK Central Repository, which..." and add, "Additionally, we would like to send urine samples to the Repository from Visits 2 (1b), 3, 4 and 5."</p> <p>Change the Biological Sample part of consent to read, "The amount of extra blood will be about 1 teaspoon to 1 tablespoon depending upon your child's weight. The total amount of blood at Study Visits 2 (1b), 3, 4 and 5 including optional repository samples will be approximately 1 to 2 tablespoons depending on your child's weight."</p> <p>Under the section, "OPTIONAL Genetic Sample", the section should state, "The amount of extra blood will be approximately 1 to 2 teaspoons." and, "The total amount of blood for Study Visit 2 (1b) including the optional repository samples will be approximately 1 to 1 ½ tablespoons depending on your child's weight."</p> <p>NOTE: Consent form template provided to you on CD refers to "fingernail clippings" and "(about 5</p>

			hairs).” The protocol is general and states, “nail clippings” and “hair samples”. To be specific on the consent form, the Biological Sample part of the consent should be changed to state, “We would also like to send a sample of your child’s fingernail/toenail clippings and a sample of your child’s hair (about 20 fibers) from Visit 2 (1b) to the same Repository.” 6. Keep your IRB preferred Confidentiality language.
14-15	A Laboratory/Specimen Working Group has been established (Section 3.6.4.3 of the protocol)	Suggestion to add a Laboratory/Specimen Working Group as a study-wide subcommittee.	No change needed to consent
16	“Submission of a concept sheet requires that (a) key personnel are certified in the NIH OHSR or equivalent training course, and (b) local IRB approval will be obtained.”	To expedite the process of concept sheet submission.	No change needed to consent
17	Deletion of, “If a writing committee member does not actively participate in the writing and/or review process,..” and Addition of, “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..”	Suggestion to revise the criteria for removing members of the writing committee	No change needed to consent
19	Table 4.2 eGFR divisions and corresponding text changed: from 40-60 to 40-59, and from 30-40 to 30-39	To clarify the divisions of the estimated GFR	No change needed to consent
20	1. 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; 2. Children aged 1-16 years, inclusive, are eligible; 3. Eligibility details modified to state that eligibility will be determined by obtaining two estimated GFR measurements, with a value between 30 to 75 ml/min/1.73m ² . The first measurement must be within the past six months and the second measurement within the past twelve months; 4. Clarified adolescent males as those greater than or equal to 13 years old (p.20 and 37)	1. Suggestion to include these groups to make our study population more representative of the general population, as long as the majority of study data can be collected 2. The Steering Committee believes that allowing 16-year-olds to participate will not compromise study data, and will help the study reach the recruitment goal 3. To provide a more specific time range for GFR measurements. 4. To clarify what age is considered “pre-pubertal” and “adolescent” in order to ensure accurate calculation of estimated GFR	1. No change needed to consent 2. Change wording to “Children between the ages of 1 and 16 years (before 17th birthday) with mild to moderate CKD may join this study.” 3. No change needed to consent 4. No change needed to consent
21	Details added to exclusion criteria regarding history of cancer, HIV, pregnancy, allergy to Iohexol, and mental retardation.	Suggestion to further refine and clarify the eligibility criteria of study participants.	No change needed to consent

22	Two estimated GFR measurements, with a value between 30 to 75 ml/min 1.73m2, will be required for study enrollment. The first measurement must be within the past six months and the second measurement within the past twelve months.	To provide a more specific time range for GFR measurements.	No change needed to consent
24	The protocol has been changed to state, “Each year, the participating child will be given a small gift, such as a gift certificate, ...”	We will provide a book store gift certificate instead of a book to allow children more choice in their book selection.	“A small gift, such as a gift certificate, will be given to your child at each study visit.”
28	Changes made to Table 5.4.2a: 1. Added footnote d 2. Added a footnote to explain the “neuropsychological assessments for high-risk children” listing in the table 3. Family Binder to be sent out before each visit 4. Diet history added to table 5. Pregnancy tests clarified as local pregnancy tests	1. Added footnote d to clarify option of obtaining local BMP and urine tests in addition to central tests; 2. “Neuropsychological assessments for high-risk children” explained in footnote to condense table; 3. Suggestion that Family Binders before each visit will help participants remember their appointment, explain the visit, and tell them what information to bring from home; “Participant” Binder changed to “Family” Binder since parent/legal guardian participates in study 4. Diet history was not listed in the previous version of the table 5. Clarification was needed about where pregnancy tests will be run	1. No change needed to consent 2. No change needed to consent unless you are from JHU, University of North Carolina, or Montefiore Medical Center– then add, “We will ask some children who are considered “high risk” for neurocognitive impairment to undergo about 1 hour of additional testing depending on his/her age. These additional instruments will look at different types of memory, problem solving, verbal and non-verbal efficiency, visual and spatial skills, and language abilities.” 3. Under “What will happen if you join this study?” add “A) Receive pre-study material” and include the wording, “You and your child will be given a Family Binder before each study visit which may include items such as a study brochure, an outline of study visits, scheduling information for the visits (dates, times, directions), instructions on what to bring to the visit (for example, information you may need to look up at home such as your child’s birth weight), a copy of this signed consent form, and a copy of some of the forms for you and your child to complete if you would like to start them before the study visit.” NOTE: Adding this will change the letter headings that follow. Change table to delete “Participant Binder” at Pre-Study to “Family Binder” 4. No change needed to consent 5. No change needed to consent
29	1. Reformatted timetable for collection of repository samples; 2. Added footnote c regarding genetic specimen	1. To clarify that “Biological Specimens” include hair, nails, blood and urine and to change the collection of the Biological Specimens to V1b 2. Suggestion to make reasonable effort to collect Genetic Blood Specimen at another visit	1. As stated above, change table to have Optional-Biological blood and urine samples to Visits 2(1b),3,4,&5. Add a row titled Optional- Biological hair and nail samples and place the X at Visit 2 (1b). 2. Information for coordinators – optional to add this to consent.

		if not collected at V1b	
32	Removed from Section 6.1: “Additionally, there will be semi-annual follow-up telephone contacts”	Suggestion to delete semi-annual follow-up telephone contacts to simplify the procedures for the coordinator and to maintain the focus of the study on patients with chronic kidney disease.	Consent form template did not include this. If your IRB requested this information in your consent, it can be deleted.
33	1. Amended Section 6.1.3 regarding assessment of Physical Activity; 2. We will now be using physical activity questions from the 2005 Youth Risk Behavior Survey (YRBS).	Suggestion that previous-day recall may not be as accurate as answers obtained with the more general YRBS	1. No change needed to consent 2. No change needed to consent
34	Nail clippings and hair samples to be collected at visit 1b	Changed from V1a; eases the burden on the study coordinator at V1a	Changes to biological sample section and table as listed above
35	Core tests to include urine creatinine	Suggestion to include this important test as a standardized core procedure	No change needed to consent.
37	For clinical sites requiring immediate results, serum creatinine will be obtained locally as part of the basic metabolic panel.	Suggestion to clarify the visit at which serum creatinine will be measured	No change needed to consent. NOTE: Consent does state that blood volumes are approximate, so including a local serum creatinine would only add less than ½ teaspoon of blood to total blood draw.
38-39	1. Details added to first morning urine collection 2. For clinical sites requiring immediate results, the protein to creatinine ratio will be obtained locally	1. To provide details regarding collection of urine if container is not provided by clinical site, and if urine is not collected at home 2. To clarify that the protein to creatinine ratio may be obtained locally if the site requires immediate results	1. Add to Study Visits 1(1a), 3, 4, and 5, “Your child will need to bring a first morning urine sample in any clean container. We will obtain a urine sample if you do not bring in a first morning urine sample.” NOTE: Add this to all Study Visits – including Visit 2 (1b) if Optional Biological consent signed 2. No change needed to consent.
39	1. Basic metabolic panel and serum glucose labs are obtained locally only if immediate results are needed 2. A BMP will be run centrally at baseline and at all annual visits. Serum glucose will be measured centrally at baseline and at all annual visits 3. Added to Section 6.2.1.7: “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.” 4. Added section 6.2.1.1 to detail Urine Pregnancy Test	1. Suggestion to include provision of an optional BMP should the local PI want immediate results 2. Suggestion to clarify the visits at which the basic metabolic panel and serum glucose will be obtained 3. Suggestion that CBC results from past 30 days will be adequate for the study and will lessen the burden on patient and local site 4. Suggestion to include details to clarify frequency of pregnancy testing and handling of positive pregnancy tests	1. No change needed to consent. NOTE: As above - Consent does state that blood volumes are approximate, so including a BMP would only add less than ½ teaspoon of blood to total blood draw. 2. No change needed to consent. 1. No change needed to consent. 2. No change needed to consent.

41	<p>1. The Abbreviated, not Screener, version of the Wechsler Individual Achievement Test-Second Edition will be used;</p> <p>2. Alpern-Boll Developmental Profile II (DP-II) has been removed from the battery of tests;</p> <p>3. CDI and BRIEF added to core tests for behavioral assessment (p. 41 and 45)</p> <p>4. The Behavior Assessment System for Children-Second Edition (BASC-2) will be used in place of the BASC (p. 41 and 44)</p>	<p>1. The WIAT-II-A comprises three key subtests that best represent the core domains of reading, writing, and arithmetic.</p> <p>2. Suggestion from the neurocognitive subcommittee to remove the DP-II since it is currently being revised. The subcommittee felt that it would be best not to use an instrument that will be considered outdated by the time CKiD is over;</p> <p>3. Suggestion from the neurocognitive subcommittee to use the most updated version;</p> <p>4. Suggestion to clarify the BASC test to be used as BASC-2.</p>	<p>1. No change needed to consent.</p> <p>2. Delete this test from your list of neurocognitive tests.</p> <p>3. Add the CDI to the list of neurocognitive tests under those completed by the child: Children's Depression Inventory (7 to 16 year old children)- assesses depression symptoms in your child Add to the list of tests completed by the parent: Behavior Rating Inventory for Executive Functions-Preschool Version (BRIEF-P) (Parents of children 2 to 6 years old)- assesses your child's patterns of behavior Also add to the list of tests completed by the parent: Behavior Rating Inventory for Executive Functions (BRIEF) (Parents of children 6 to 16 years old)- assesses your child's patterns of behavior</p> <p>4. No change needed to consent</p>
41, 45	The Child Behavior Checklist (CBCL) has been removed from the battery	Steering Committee feels that other surveys will be more comprehensive than the CBCL	Delete this test from your list of neurocognitive tests
42	Minor rewording to Section 6.3.1.1.1;	To clarify that the Mullen Scales of Early Learning is a measure of development and cognitive function and that children over the age of 29 months will not receive the Mullen Scales of Early Learning	Mullen Scales are for 12-29 month olds. Consent template had incorrectly read 1-29 months.
43	Description of Alpern-Boll Developmental Profile II removed	The Alpern-Boll Developmental Profile II has been removed from the neurocognitive battery of tests	As above, delete this test from the list of neurocognitive tests
44	Diagram 6.3.1.2 amended by removing CBC-L and adding the CDI, BRIEF-P, and BRIEF	To make the diagram reflect the changes in the neurocognitive battery of tests	If your IRB required a table for neurocognitive tests, these tests can be deleted.
45-46	<p>1. Added descriptions of Children's Depression Inventory (CDI), Behavior Rating Inventory for Executive Functions – Preschool Version (BRIEF-P), and Behavior Rating Inventory for Executive Functions (BRIEF)</p> <p>2. The Clinical Evaluation of Language Fundamental- 4th Edition (CELF-4) will be administered</p>	<p>1. To provide PI's, study coordinators, psychologists, and IRB officials with in-depth details of each of the new additions to the neurocognitive battery</p> <p>2. To clarify the specific CELF test that will be administered</p>	<p>1. As above, Add the CDI to the list of neurocognitive tests under those completed by the child: Children's Depression Inventory (7 to 16 year old children)- assesses depression symptoms in your child Add to the list of tests completed by the parent: Behavior Rating Inventory for Executive Functions-Preschool Version (BRIEF-P) (Parents of children 2 to 6 years old)- assesses your child's patterns of behavior Also add to the list of tests completed by the parent: Behavior Rating Inventory for Executive Functions (BRIEF) (Parents of children 6 to 16 years old)- assesses your child's patterns of behavior</p>

			2. No change needed to consent.
55	Details added about fasting but not thirsting before lipid studies	To clarify instructions for fasting but not thirsting	Delete from Study Visits 3 and 5, “Also, your child should not eat before the first blood draw (drinking water is alright).” Replace with, “Your child will need to refrain from eating after midnight the night before this visit and prior to the first blood draw. Your child may drink water or zero-calorie beverages that are non-caffeinated and may chew sugar-free gum.”
58	<p>1. Three-day diet records will be obtained on a yearly basis beginning at the second baseline visit (V1b);</p> <p>2. 3-day diet history must include two weekdays and one weekend day;</p> <p>3. Written food records will be sent from the parents to the clinical site study coordinator, not directly to the DCC;</p> <p>4. Added the sentence, “Only select clinical sites will perform bone biopsies.”</p>	<p>1. Suggestion to modify the timing of the 3-day diet record to visit 1b to give the coordinator or dietician a chance to explain the procedure at visit 1a.</p> <p>2. Diet of 2 weekdays and 1 weekend day will be most representative of overall diet</p> <p>3. This procedure will reduce the burden on parents</p> <p>4. To highlight the fact that bone biopsies will not be done at each clinical site</p>	<p>1. No change needed to consent</p> <p>2. No change needed to consent</p> <p>3. No change needed to consent</p> <p>4. No change needed to consent</p>
78	New study coordinators will be able to review a training video, but not necessarily the video of the training meetings that took place in Nov 2004	Plans are being made to assemble a DVD highlighting the major components of the CKiD protocol and study visits	No change needed to consent
83	Added, “It is recommended that a follow-up letter documenting information discussed by phone should also be sent to the participant’s primary nephrologists.”	Suggestion to modify the wording of the follow-up process for immediate alerts since the CKiD study will not track this information	No change needed to consent
84	Deletion of the sentence, “It is also recommended that BP and Pulse be monitored hourly after the Iohexol injection for the course of the study visit.”	BP and Pulse will be monitored in accordance with recommendations of the Steering Committee.	No change needed to consent

86	<p>1. The repositories have been added to the group of centers that have the responsibility to maintain confidentiality</p> <p>2. The DCC, clinical coordinating centers and repositories do not have access to the log kept at the clinical sites that has participant names, participant ID numbers, and pertinent registration information</p>	<p>1. Suggestion to include the repositories in the group of centers that are responsible for maintaining confidentiality. This will clarify that they maintain confidentiality like the clinical sites, the clinical coordinating centers, and the DCC.</p> <p>2. Suggestion to clarify that the logs will only be accessible to the clinical sites.</p>	<p>1. Based upon the consent form template, no change is needed to the consent; however, this may be site specific if you added this information to your consent.</p> <p>2. No change needed to consent</p>
86-87	A Certificate of Confidentiality will be obtained for the entire study from the National Institutes of Health.	Suggestion to add information regarding the Certificate of Confidentiality	Site specific
88	Laboratory/Specimen Working Group added	To identify the members of this subcommittee	No change needed to consent

92	Appendix E removed from protocol	Suggestion to remove Appendix E from the protocol. These alerts will be captured on the clinical research forms and will be reported to the appropriate personnel as indicated on pages 83-84.	No change needed to consent
Throughout the protocol		Suggestion to make minor grammatical changes throughout the protocol	No change needed to consent.
	REQUIRED CONSENT FORM CHANGES		
	In the section of the consent headed "To Study kidney function" Delete the sentence, "Your child will be asked to eat a low-protein diet 24 hours before the GFR. Low-protein diet instructions will be provided." Remove the information about the low-protein diet from Study Visits 1, 3 and 5. Consent form template and MOP included the low-protein diet; although protocol did not.		
	Under the section, "To study brain development and behavior" Remove the Visual Analog Scale from the list of neurocognitive tests. Consent form template provided to you on CD included this test; although protocol did not		
	Under the section, "Are there risks related to pregnancy?" Delete the wording "or fathered a child". Consent form template provided to you included this wording; although protocol did not and we are not tracking this information		
	Under "To study brain development and behavior" Add, "You will receive written feedback about your child's performance on the cognitive tests. Your nephrologist will also receive a copy of this feedback. You will also be informed, through your nephrologist, if your child's answers suggest the possibility of self-injury or injury to others."		

26.3 CONSENT FORM January 2007 AMENDMENT:

CKiD Consent Form Table-lists the changes from 01/01/06 version of the Consent Form Template to 01/01/07

* All changes to original text will be printed in *italics* *

Page #(s) on 04/01/05 version of Consent Form Template	Change to Consent Form	Required or Recommended Changes
1	In the section under “Why is this research being done”: 1) CHANGE: About 540 children will be in this study at 51 different places...	Recommended
2	In the section under “Attend up to five study visits”: 1) CHANGE: For children over the age of 3, Study Visit 1B will be <i>within six months</i> after Study Visit 1A. 2) CHANGE: If we notice during the <i>study</i> your child’s kidney function has become a lot worse, we will ask you to come back <i>within six months for your next study visit.</i> 3) CHANGE: Study visits 2, 3, and 4 will take place annually after Study Visit 1A	Recommended
2	In the section under “To study kidney function”: ADD the following sentence: <i>If we are unable to obtain the GFR you may be asked to reschedule the study visit.</i>	Recommended
3	In the section under “To study brain development and behavior”: 1) ADD the following sentence: <i>If the Neurocognitive testing data can not be obtained during the child’s scheduled study visit, these measurements will be scheduled within +/- one month of the scheduled visit.</i>	Recommended
3	In the section under “To study heart function”: 1) ADD the following sentence: <i>If the ECHO, Ambulatory Blood Pressure Monitoring (ABPM) can not be obtained during the child’s scheduled study visit, these measurements will be scheduled within +/- one month of the scheduled visit.</i> 2) CHANGE: Your child will wear the ABPM for 24 hours.	Recommended
3	In the section under “To study growth”: 1) DELETE the following sentences: The parent/legal guardian or child if appropriate will keep a three-day diet record each year. From this three-day diet record, you will have the option of obtaining data from your child’s school (type of lunch, nutrition information, etc.) to help make this diet history more complete. 1) ADD the following sentence: <i>We will obtain dietary intake information each year.</i>	Required
4	In the section under “Complete a variety of forms”: 1) DELETE: “...a 3-day diet history of your child;” 2) ADD: “...dietary habits;” NOTE: Remove any references to the 3-day diet history that may be in your consent form	Required
4	In the section under “OPTIONAL Biological Sample:” 1) ADD the following sentence: <i>If the nail clippings and hair samples are not collected at V1b, then the sample will be collected and shipped at the next study visit. .</i>	Recommended
4	In the section under “OPTIONAL Genetic Sample:” 1) ADD the following sentence: <i>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.</i>	Recommended
	NOTE: Study Protocol and East Coast CCC label study visits as: Visit 1A, Visit 1B, Visit 2, Visit 3, and Visit 4 The MidWest CCC label study visits as: Visit 1, Visit 2, Visit 3, Visit 4, and Visit 5	

26.4 CONSENT FORM 2008 AMENDMENT

26.4.1 CONSENT FORM AMENDMENT: April 2008

The Consent Form Table below lists the changes made to the 01/01/07 version of the Consent Form Template. You may need to change the page numbers in the table below to match the page numbers in your approved consent form **All changes to original text will be printed in italics.* Recommended changes are only suggestions and do not have to be implemented in your consent form.

Page #(s) on 01/01/07 version of the CKiD Consent Form Template	Changes to Consent Form	Required or Recommended Changes
Page 1	Changed the Version date of the Consent Form Template to 04/15/08 to indicate the latest revised version.	Required
Page 1	Under the section “What you should know about this study” In the last bullet, DELETE the words: <i>If children may join this study</i>	Recommended
Page 1	In the section under “Why is this research being done” REWORD the sentence: <i>About 540 children from 50 different places around North America have now joined the study.</i> ADD the following sentence: <i>We would like to have 60 more children of African American descent join this study so that our study group will closely represent all children in North America with CKD.</i> ADD the following sentence: <i>If you have already joined this study, we are asking you to continue your participation until July 31st, 2013, so we can continue to learn more about what factors cause CKD to get worse in children.</i>	Recommended Recommended Recommended
Page 1	Under the section titled “What will happen if you join this study?” ADD the phrase in italics to this sentence: <i>If you agree to be in this study, or continue participating for another 5 years (until July 31st, 2013), we will ask you to do the following things:</i>	Recommended
Page 2	In the section under “Attend up to five study visits” CHANGE the title to: Attend up to <i>nine</i> study visits CHANGE these sentences: Each participant will be in this study for about <i>five</i> to <i>eight</i> years. (If you enter the study in the <i>fifth</i> year after the study has started, you will only have the first <i>six</i> study visits in <i>five</i> years). ADD the study visits in italics to the following sentence: The length of the study visits are as follows:..... <i>Visit 5 – about 4 hours; Visit 6 – about 7 hours; Visit 7 – about 4 hours; Visit 8 – about 7 hours.</i> ADD the study visits in italics to the following sentence: Study visits 2, 3, 4, <i>5, 6, 7</i> and <i>8</i> will take place annually after Study Visit 1A. CHANGE the sentence: If we notice during the study that your child’s kidney function has become a lot worse, we will ask you to come back <i>sooner for your next study visit before your child starts dialysis or has a kidney transplant.</i> ADD the following sentences: <i>We may ask to measure your child’s kidney function at this visit, if it has</i>	Required Required Required Required Recommended

	<i>been more than 3 months since their last measurement in the study. This will be your child's last study visit.</i>	Recommended
Page 3	In the section under "To study kidney function" ADD the following sentence: <i>When you reach the 5th study visit, we will decrease the number of time points from four to three.</i> ADD "iron" to the sentence: Blood and urine tests such as (Creatinine and Iron) will also be done to measure kidney function at each study visit.	Recommended Recommended
Page 3	In the section under "To study brain development and behavior" ONLY ADD the following tests here, if your site is required by the IRB to list all neurocognitive tests in your consent form. <ul style="list-style-type: none"> a. <i>Delis Kaplan Executive Function System (D-KEFS Tower) – will be administered to children 6yrs and older.</i> b. <i>Weschler Intelligence Scale for Children, Fourth Edition (WISC-IV) – will be administered to children 6yrs and older.</i> c. <i>Weschler Adult Intelligence Scale, Third Edition (WAIS-III) - will be administered to children 17yrs and older.</i> ONLY DELETE the following tests, if your site is required by the IRB to list all behavioral tests in your consent form. <ul style="list-style-type: none"> a. <i>Children's Depression Inventory (CDI) – administered to children 7 – 17yrs old</i> b. <i>Behavior Assessment System for Children, 2nd Edition – Self Report of Personality (BASC-2 SRP) – administered to children 8 – 21yrs old</i> c. <i>Adaptive Behavior Assessment System 2nd Edition (ABAS-II)- administered to parents of children 0 – 21yrs old</i> 	Only required if mandated by your IRB Only required if mandated by your IRB
Page 3	Under the section titled "To study brain development and behavior" DELETE the information regarding high-risk cognitive testing as only 3 sites (site 50, 60 and 64) are currently participating in this sub study.	Not Applicable to most clinical sites
Page 3	Under the section titled "To study heart function" In the 2 nd paragraph, ADD study visits 6 and 8 to this sentence: For study Visits 2, 4, 6 and 8 , we will use Ambulatory Blood Pressure Monitoring to look for	Required
	In the 3 rd paragraph, ADD study visits 6 and 8 to this sentence: At Study Visits 2, 4, 6 and 8 , we will use this to find abnormalities of the heart.	Required
Page 3	Under the section titled "To study growth" ADD waist and hip circumference to the sentence: We will measure height, weight, waist and hip	Recommended

	<p><i>circumference</i> during a physical exam at every study visit. DELETED the information regarding bone biopsies as they are not being performed as part of the core CKiD study.</p>	Not Applicable to most sites
Page 4	<p>In the section under “OPTIONAL Biological Sample”</p> <p>ADD the following sentences: <i>At visit 4, we would also like to send an additional sample of your child’s toenail clippings to the same Repository. If the toenail clippings are not obtained at visit 4, they will be collected and shipped at your next study visit.</i></p>	Required
Page 6	<p>In the section entitled “Will you be paid if you join this study?”</p> <p>ADD compensation for additional visits: <i>\$75 for completion of Study Visit 5, \$150 for completion of Study Visit 6, \$75 for completion of Study Visit 7 and \$150 for completion of Study Visit 8.</i></p> <p>ADD ‘may’ to the sentence: A small gift, such as a gift certificate, <i>may</i> be given to your child at each study visit.</p>	Required Recommended
Page 11	<p>Update the CKiD Study Timetable: ADD the approximate length/time of the study visits to the table ADD collection of biological toenail samples at visit 4 ADD schedules and procedures to be done at Visits 5, 6, 7 and 8</p>	Required Required

26.4.2 CONSENT FORM AMENDMENT: July 2008

The Consent Form Table below lists the changes made to the 04/15/08 version of the Consent Form Template. You may need to change the page numbers in the table below to match the page numbers in your approved consent form **All changes to original text will be printed in italics*. Recommended changes are only suggestions and do not have to be implemented in your consent form.

Page #(s) on 04/15/08 version of the CKiD Consent Form Template	Changes to Consent Form	Required or Recommended Changes
Page 1	Changed the Version date of the Consent Form Template to 07/01/08 to indicate the latest revised version.	Required
Page 3	<p>In the section under “To study brain development and behavior”</p> <p>ONLY ADD the following tests here, if your site is required by the IRB to list all neurocognitive tests in your consent form.</p> <p><i>d. Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) - will be administered to children 17yrs and older.</i></p> <p>ONLY DELETE the following test, if your site is required by the IRB to list all neurocognitive tests in your consent form.</p> <p><i>d. Wechsler Individual Achievement Test Second Edition-Abbreviated (WIAT-II-A) – administered to children 6 yrs old</i></p>	<p>Only required if mandated by your IRB</p> <p>Only required if mandated by your IRB</p>

26.5 CONSENT FORM AMENDMENT: December 2009

The Consent Form Table below lists the changes made to the 07/01/08 version of the Consent Form Template. You may need to change the page numbers in the table below to match the page numbers in your IRB approved consent form **All changes to original text will be printed in italics*. Recommended changes are only suggestions and do not have to be implemented in your consent form.

Page # on the 07/01/08 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED or Recommended Changes
Page 1	Change the Version date to 12/01/09 to indicate the latest revised version.	REQUIRED
Page 1	<p>In the section titled “2. Why is this research being done?”</p> <p>Revise the following sentence in the 1st paragraph: The number of people with CKD continues to grow, and about 650,000 Americans will have <i>ESRD</i> by the year 2010.</p>	REQUIRED
Page 3	<p>In the section titled “2. To study brain development and behavior”</p> <p>ONLY ADD the following tests here if your site is required by the IRB to list all the behavioral tests in your consent form.</p> <ul style="list-style-type: none"> <i>e. Behavior Assessment System for Children, 2nd Edition Self Report of Personality (BASC-2 SRP) – administered to participants 21yrs to 25yrs old</i> <i>f. Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A) – administered to participants 18yrs and older</i> <i>g. Short Form with 36 Questions Self-Report (SF-36) – administered to participants 18yrs and older</i> 	Only REQUIRED if mandated by your IRB
Page 3	<p>Under the section titled “3. To study heart function”</p> <p>In the 3rd paragraph, ADD the following sentence: <i>If the ABPM cannot be obtained within one month of the visit, you may be asked to return to the clinic so that your child’s manual blood pressure can be checked again so that it can be compared to the ABPM results.</i></p>	Recommended
Page 4	<p>In the section under “F) i. OPTIONAL Biological Sample”</p> <p>ADD visits 5, 6, 7 & 8 to the following 2 sentences in the first paragraph:</p> <p>We would like to draw a small amount of blood (about 1 – 2 teaspoons depending on your child’s weight) at Visit 1B, 2, 3, 4, 5, 6, 7 and 8 that will be sent to the NIDDK...</p> <p>Additionally, we would like to send urine samples to the Repository from Visits 1B, 2, 3, 4, 5, 6, 7 and</p>	REQUIRED

	<p>8.</p> <p>CHANGE the blood volume amount in the following sentence: The amount of extra blood will be about 8 to 16 teaspoons over the entire study depending upon your child’s weight.</p> <p>ADD visits 5 – 8 and update the blood volume amount in the following sentence: The total amount of blood for Study Visit 1B, 2, 3, 4, 5, 6, 7 and 8 including the Biological Sample will be approximately 3 to 7 teaspoons per visit depending on your child’s weight.</p>	<p>REQUIRED</p> <p>REQUIRED</p>
Page 5	<p>In the section under “F) ii. OPTIONAL Genetic Sample”</p> <p>CHANGE the blood volume unit in the following sentence: The amount of blood for Study Visit 1B including the Biological and Genetic Sample will be about 3 to 4 <i>teaspoons</i> depending upon your child’s weight.</p>	REQUIRED
Page 9	<p>In the section titled “14. d What happens to Data, Tissue, Blood and Samples that are collected in the study?”</p> <p>Reword and re-format the following sentences: If you join this study,</p> <ul style="list-style-type: none"> • <i>You will not own the data, or tissue, blood or other specimens given by you to the investigators for this research.</i> • <i>Both Clinical Site Name and any sponsor of the research may study your data and the tissue, blood or other specimens collected from you.</i> • <i>If data, tissue, blood or other specimens are in a form that identifies you, Clinical Site Name may use them for future research only with your consent of IRB approval.</i> • <i>You will not own any product or idea created by the researchers working on this study.</i> • <i>You will not receive any financial benefit from the creation, use or sale of such a product or idea.</i> 	REQUIRED
Page 11	<p>Revise the CKiD Study Timetable to provide better clarification for when visits should occur. The timing of visits 1B through 8 are determined based on when VIA occurred.</p> <p>In the column titled Study Visit 3, change 1 year after Visit 2 to read 2 years after VIA In the column titled Study Visit 4, change 1 year after Visit 3 to read 3 years after VIA In the column titled Study Visit 5, change 1 year after Visit 4 to read 4 years after VIA In the column titled Study Visit 6, change 1 year after Visit 5 to read 5 years after VIA In the column titled Study Visit 7, change 1 year after Visit 6 to read 6 years after VIA In the column titled Study Visit 8, change 1 year after Visit 7 to read 7 years after VIA</p>	Recommended

26.6 CONSENT FORM AMENDMENT: November 2010

The Consent Form Table below lists the changes made to the 12/01/09 version of the Consent Form Template. You may need to change the page numbers in the table below to match the page numbers in your IRB approved consent form **All changes to original text will be printed in bold italics*. Recommended changes are only suggestions and do not have to be incorporated into your consent form.

Page # on the 12/01/09 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED or Recommended Changes
Page 1	Change the Version date to 11/01/10 to indicate the latest revised version.	REQUIRED
Page 1	<p>In the section titled “2. Why is this research being done?”</p> <p>Update the statistics in the following sentence in the 1st paragraph: The number of people with CKD continues to grow, and about 785,000 Americans will have ESRD by the year 2020.</p> <p>Update the target enrollment number and total sites in the following sentence in the 3rd paragraph: About 880 children between the ages of 1 and 16yrs (before 17th birthday), with mild to moderate CKD and from 50 different places around North America will be in this study.</p> <p>Add the following sentence to the last paragraph in this section: <i>We would also like to inform you of some minor changes to the study</i></p>	<p>REQUIRED</p> <p>REQUIRED</p> <p>Recommended</p>
Page 2	<p>In section 3 titled, “What will happen if you join this study?” under sub-section A) Receive pre-study material</p> <p>Revise the 1st sentence which states: You and your child will be given <i>instructions</i> prior to each study visit which will include a study brochure,.....etc.</p> <p>Under sub-section B) Attend up to 9 study visits</p> <p>Revise the number of years in following sentences: Each participant will be in this study for about <i>three</i> to eight years. (If you enter the study in the <i>eighth</i> year after the study has started, you will only have the first <i>four</i> study visits in <i>three</i> years.)</p>	<p>Recommended</p> <p>REQUIRED</p>
Page 2	<p>In the section titled “1. To study kidney function”</p> <p>Revise the following sentences which explain the changes to the GFR procedure: Your child will come to <<ENTER LOCATION>> in the morning and an IV catheter <i>may</i> be placed.</p> <p>Study bloodwork <i>may</i> then be drawn from the IV <i>or through separate needlesticks or fingersticks, if you prefer</i>.</p> <p>Delete medication from this sentence as Iohexol is not used for treatment: A non-radioactive x-ray dye medication (Iohexol, brand name, Omnipaque®) will then be given</p>	<p>Recommended</p> <p>Recommended</p> <p>REQUIRED</p>

	<p>Then we will take a small amount of blood (less than ¼ teaspoon) from the IV at 2 points in time after the Iohexol is given. The blood samples can <i>also</i> be obtained through 2 separate needle-sticks or finger-sticks <i>instead of the IV</i> if preferred.</p> <p>Delete this next sentence as all Iohexol GFR measurements will now be determined using 2 time points. <i>When you reach the 5th study visit, we will decrease the number of time points from four to three.</i></p> <p>Delete iron from the last sentence in this section which states: Blood and urine tests (such as creatinine and iron) will also be done to measure kidney function at each study visit.</p>	<p>REQUIRED</p> <p>REQUIRED</p> <p>REQUIRED</p>
Page 3	<p>In the section titled “2. To study brain development and behavior”</p> <p>ONLY ADD the following test here if your site is required by your IRB to list all the behavioral tests in your consent form.</p> <p><i>h. Pediatrics Quality of Life Scale (PedsQL) Young Adult – administered to participants 18yrs and older</i></p> <p>ONLY DELETE the following test here if your site is required by your IRB to list all the behavioral tests in your consent form.</p> <p><i>a. Short Form with 36 Questions Self-Report (SF-36) – administered to participants 18yrs and older</i></p> <p>Revise the last sentence in this sub-section which states: If the Neurocognitive testing data cannot be obtained during the child’s scheduled study visit, these measurements <i>should</i> be scheduled within +/- one month of the scheduled visit.</p>	<p>Only REQUIRED if mandated by your IRB</p> <p>Only REQUIRED if mandated by your IRB</p> <p>Recommended</p>
Page 3	<p>In the section titled, “D) Complete a Variety of Forms”</p> <p>ADD information about health literacy and numeracy to this sub-section: We will ask you and your child to complete several forms that ask for information about: you and your child’s age, sex, race/ethnicity, education and household income; your child’s medical history, <i>your health literacy and numeracy</i>, your child’s birth and family history (birth weight, length, gestational age,.....etc.</p>	<p>REQUIRED</p>
Page 4	<p>In the section under “F) i. OPTIONAL Biological Sample”</p> <p>Revise the text and update the amount of blood in the 2nd last sentence of the 1st paragraph: <i>If all study visits are completed</i>, the amount of extra blood will be 9.5 to 16 teaspoons over the entire study depending upon your child’s weight</p> <p>CHANGE the amount of blood in the last sentence of the 1st paragraph: The total amount of blood for Study Visit 1B, 2, 3, 4, 5, 6, 7 and 8 including the Biological Sample will be approximately 4 to 7 teaspoons per visit depending on your child’s weight.</p>	<p>REQUIRED</p> <p>REQUIRED</p>

26.7 CONSENT FORM AMENDMENT: **September 1, 2012**

The Consent Form Table below lists the changes made to the 11/01/10 version of the Consent Form Template. You may need to change the page numbers in the table below to match the page numbers in your IRB approved consent form **All changes to original text will be printed in italics.* Recommended changes are only suggestions and do not have to be implemented in your consent form.

Page # on the 9/1/12 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Changes
Page 1	Updated Version of Consent Template: 9/1/12	REQUIRED
Page 1	DELETED: the National Institute of Neurological Disorders and Stroke (NINDS).	REQUIRED
Page 1	DELETED: We would also like to inform you of some minor changes.	OPTIONAL
Page 2	ADDED: <i>“Depending on when you enter the study, you may be in this study for up to 8 years (until July 31st, 2013); however, we plan to extend the study so that it is possible to be in the study for up to 13 years (until July 31, 2018).”</i> In the next sentence DELETED: “ for another 5 years until July 31 st , 3013”	RECOMMENDED
Page 2	Updated wording of coordinator instructions: << NOTE: STUDY PROTOCOL LABELS STUDY VISITS AS: VISIT 1A, VISIT 1B, VISIT 2, VISIT 3, VISIT 4.....THROUGH VISIT 9. SOME IRBS MAY REQUIRE YOU TOLABEL STUDY VISITS ACCORDING TO THE NUMBER OF TIMES THE SUBJECTS COMES IN FOR VISIT: VISIT 1, VISIT 2, VISIT 3, VISIT 4, VISIT 5.....THROUGH VISIT 10>>	N/A
Page 2	<< NOTE: OMIT OR DELETE THE NEXT PARAGRAPH IF IT DOES NOT PERTAIN TO YOUR SUBMISSION. DELETED: “three”, and “four” ADDED: “There will be one study visit per year except during the first year when there will be two study visits. Each participant will be in this study for about <i>one</i> to eight years. (If you enter the study in the eighth year after the study has started, you will only have the first <i>two</i> study visits in <i>one</i> year). <i>If the study is extended until 2018 a participant could have up to 12 visits.</i> ”	OPTIONAL (only if required by your IRB)
Page 2	Simplified wording. Deleted: “Visit 1A - about 7 hours; Visit 1B – about 4 hours; Visit 2 - about 7 hours; Visit 3 - about 4 hours; Visit 4 - about 7 hours; Visit 5 – about 4 hours; Visit 6 – about 7 hours; Visit 7 – about 4 hours and Visit 8 – about 7 hours.” ADDED: <i>“Visit (1A, V2, V4, V6, V8 ...etc.) about 7 hours; Visit 1B (V1B, V3, V5, V7, V9 ...etc.) – about 4 hours.”</i>	RECOMMENDED
Page 2	Simplified wording. DELETED: “2, 3, 4, 5, 6, 7 and 8” ADDED: <i>“Study visits beginning with the V2 will take place annually after Study Visit 1A.”</i>	RECOMMENDED

Page 2	Protocol change to define subjects eligible for irregular visits. ADDED: “If you <i>will be unable to attend future study visits, or</i> we notice during the study that your child’s kidney function has become a lot worse, we will ask you to come back sooner for your next study visit. DELETED: “before your child starts dialysis or has a kidney transplant”	REQUIRED
Page 2	To include PIP in main consent form: DELETED: “This will be your child’s last study visit” ADDED: “ <i>Afterwards, we would continue follow up with you on a yearly basis with Phone-In-Person Follow Up (PIP) interview. As a part of this phone call or in-person interview we will also record your child’s most recent laboratory results.</i> ”	RECOMMENDED
Page 2	For clarification ADDED: “There is a chart of <i>CKiD</i> study visits attached to the end of this form.”	RECOMMENDED
Page 3	DELETED: “take” and ADDED: “We will <i>measure</i> blood pressure...”	OPTIONAL
Page 3	Simplify language. DELETED: “For study visits 2, 4, 6, and 8” and “monitoring”. ADDED: “ <i>Every other year beginning with V2</i> , we will use <i>an</i> Ambulatory Blood Pressure <i>Monitor</i> (ABPM)...” ADDED: <i>Every other year beginning with the V2</i> an echocardiogram (<i>ECHO</i>) will be done. <i>The ECHO</i> uses ultrasound to take pictures of your child’s heart.	RECOMMENDED
Page 3	Protocol Change for sub study. ADDED: “ <i>Starting at V2, we will measure pulse wave velocity (PWV) in order to analyze the stiffness or flexibility of your arteries. PWV is a way to measure blood pressure at the heart instead of the arm. It is non-invasive. During the test a pencil-like sensor is placed on your wrist and upper leg to record blood pressure signals from your pulse. Three small sticky pads will also be placed on your chest to measure heart beats.</i> ”	REQUIRED (only for Sites Participating in Pulse Wave Velocity Sub-Study)
Page 4	Protocol Change for sub study. ADDED: “ <i>In children, eight (8) years old or older who meet the eligibility criteria, we will do a cardiac MRI of the heart. These children will be asked to complete a questionnaire to ensure they are eligible to have a cardiac MRI performed. This cardiac MRI is a safe, non-invasive test and it will be done once. The MRI uses radio waves, magnets and computers to take a picture of your child’s heart. The picture will allow us to check coronary heart disease and conditions.</i> ”	REQUIRED
Page 4	Protocol change adding new tests. ADDED: “ <i>At every other visit beginning at the V3 visit we will do a 6 minute walk test (6MWT) which is used to measure how far your child can walk in 6 minutes. The 6MWT is done indoors in an appropriate corridor using cones to mark distance.</i> ” And ADDED: “ <i>At every other visit beginning at the V3 visit we will also measure your child’s hand and forearm muscle strength. To do this, we will use a dynamometer to measure hand grip strength.</i> ”	REQUIRED

Page 4	To allow for chart review with PIP and main study ADDED: <i>“We may also collect information from your medical record. Information collected will include the following: your diagnosis, lab results, medications, hospitalizations, surgeries, and medical treatments.”</i>	REQUIRED
Page 5	Simplify language, and indicating a change in blood volume obtained. DELETED: “visits 2, 3, 4, 5, 6, 7 and 8.” In two sentences. ADDED: “We would like to draw a small amount of blood (about 2-3 teaspoons depending on your child’s weight) at <i>each study visit beginning with the 1B</i> that will...” and ADDED: “Additionally, we would like to send urine samples to the Repository from <i>each study visit beginning with the 1B.</i> ”	REQUIRED
Page 5	Indicating increased blood volume obtained. “If all study visits are completed, the amount of extra blood will be about 16 to 26 teaspoons over the entire study depending upon your child’s weight.”	REQUIRED
Page 5	Added V9 as some child will be completing this visit. “The total amount of blood for Study Visit 1B, 2, 3, 4, 5, 6, 7, 8, and 9 including the Biological Sample will be approximately 3 to 6 teaspoons per visit depending on your child’s weight.	REQUIRED
Page 6	Clarification of information. ADDED: “At 20 times the dose to be given in this study, Iohexol has caused heart rhythm problems in <i>less than 1%</i> of patients”.	REQUIRED
Page 6	Clarified statement. DELETED: “low” blood pressure ADDED: “...wheezing, <i>changes in</i> blood pressure, <i>changes in heart rate</i> , dizziness and fainting.”	REQUIRED
Page 6	Word addition. ADDED: Iohexol would not <i>be</i> used if...”	RECOMMENDED
Page 6	Changed wording on potential risk of blood draws and IV. ADDED: <i>“Blood Draws and Insertion of an Intravenous Catheters Drawing blood or inserting an IV catheter may cause some pain, bleeding or bruising at the spot where the needle enters or where the plastic tube stays in your body. Rarely, the procedure can cause fainting or infection or swelling of the vein. Sometimes, the tip of the catheter or needle could withdraw from the vein or poke through the vein causing the Iohexol to leak (infiltrate) into the surrounding tissue. This may cause some pain or swelling but there is very little risk of tissue damage. If the Iohexol infiltrates (leaks), the GFR test cannot be performed we will ask you to reschedule the test for another day. Your child’s doctors and nurses will be checking often to see if any side effects are occurring.”</i>	REQUIRED
Page 7	Protocol change of risk of test to be done as a sub-study. ADDED: <i>“Pulse Wave Velocity: 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.”</i>	REQUIRED (only for Sites Participating in Pulse Wave Velocity Sub-Study)
Page 7	Protocol change of risk of test to be done as a sub-study. ADDED: <i>“Cardiac MRI: “There are no known significant risks with a cardiac MRI. You may, however, be bothered by feelings of confinement</i>	REQUIRED

	<i>(claustrophobia), and by the noise made by the magnet during the procedure. Prior to your exam, you will be asked to complete a standard questionnaire. The purpose of this questionnaire is to ensure that you are able to safely enter the MRI area. The questionnaire and the way the MRI staff position you on the table are very important to ensure you will be safe during the MRI.”</i>	
Page 7	Protocol change of risk of new test. ADDED: “ <i><u>6 Minute Walk Test</u> There are no confirmed side effects from participating in this test.”</i>	REQUIRED
Page 7	Protocol change of risk of new test. ADDED: “ <i><u>Grip Strength</u> There are no confirmed side effects from using the grip strength instrument.</i>	REQUIRED
Page 7	Including PIP in consent. ADDED: “If the urine test indicates pregnancy, your child would be ineligible to continue with the <i>main</i> study, <i>but could participate in (PIP) follow up interviews.</i> ”	REQUIRED
Page 8	Simplified text: Added “ <i>you will receive the following:</i> ” DELETED: “we will give you” ADDED: “\$150 for completion of <i>each</i> Study Visit (1A, <i>V2, V4, V6, V8...etc,</i>) \$75 for completion of <i>each</i> Study Visit (1B, <i>V3, V5, V7, V9...etc.</i> .” DELETED: “\$150 for completion of Study Visit 2, \$75 for completion of Study Visit 3, “\$150 for completion of Study Visit 4, \$75 for completion of Study Visit 5, \$150 for completion of Study Visit 6, \$75 for completion of Study Visit 7, \$150 for completion of Study Visit 8.”	RECOMMENDED
Page 8	To include PIP in consent form. ADDED: “ <i>If you have been enrolled in the Phone-In-Person Follow Up (PIP), we will give you \$50 for each interview completed.</i> ”	RECOMMENDED
Page 9	Word addition. ADDED: Examples include government groups, safety monitors, <i>and</i> other...”	RECOMMENDED
Page 12	ADDED: C-IMT and Pulse Wave Velocity to the table of visit procedures.	REQUIRED (only if you are doing these sub-study tests)
Page 12	ADDED: Cardiac MRI, 6 Minute walk and Grip Strength to the table of visit procedures.	REQUIRED

26.8 CKiD CONSENT FORM AMENDMENT TABLE: July 1, 2013

The Consent Form Table below lists the changes made to the 9/1/12 version of the Consent Form Template. You may need to change the page numbers in the table below to match the page numbers in your IRB approved consent form **All changes to original text will be printed in bold italics*. Recommended changes are only suggestions and do not have to be incorporated into your consent form.

Page # on the 7/1/13 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Changes
Page 1	Updated Version of Consent Template: 7/1/13	REQUIRED
Page 1	Revised time period. DELETED “2013” ADDED “ 2018 ” DELETED “8” ADDED “ 13 ” DELETED “2013); however, we plan to extend the study so that it is possible to be in the study for up to 13 years (until July 31, 2018)” ADDED “ 2018 ”	REQUIRED
Page 2	Revised time period. DELETED “nine” ADDED “ 15 ” DELETED “9” ADDED “ 15 ” DELETED “...THROUGH VISIT 10” DELETED “NOTE: OMIT OR DELETE THE NEXT PARAGRAPH IF IT DOES NOT PERTAIN TO YOUR SUBMISSION” DELETED “one to eight” ADDED “ five (5) to 13 ” DELETED “(If you enter the study in the eighth year after the study has started, you will only have the first two study visits in one year). If the study is extended until 2018 a participant could have up to 12 visits.”	REQUIRED
Page 2	Revised language DELETED “with a Phone/In-Person Follow-up (PIP) interview” ADDED “ <i>This follow-up would be an interview that may be completed via phone/in-person interview or on-line survey.</i> ” DELETED “phone call or in-person” ADDED “ <i>continued follow-up</i> ”.	REQUIRED

Page 3	Revised language. DELETED: “measure pulse wave velocity (PWV) in order to analyze the stiffness or flexibility of your arteries. PWV is a way to measure blood pressure at the heart instead of the arm”. ADDED: “... <i>perform vascular tests to determine whether stiffer arteries put patients at risk for heart or kidney problems in the future. These tests do not use radiation (X-rays), sound waves (ultrasound) or needles; however, these tests give doctors information about the stiffness or flexibility of your arteries.</i> During this non-invasive procedure, you will have sticky patches placed on your chest <i>and a small instrument shaped like a pen will be placed on your wrist</i> to record your heart beat. <i>This pen-shaped instrument has a highly-sensitive sensor on one end that can detect pressure changes in the arteries. Then the same pen-shaped instrument will be placed on the side of your neck and the top of your leg to measure the speed of your pulse.</i> ”	REQUIRED (only for Sites Participating in any component of the Vascular Tests Sub-Study)
Page 3	ADDED: “ <i>Additionally, you will lie still for 10 more minutes and your heart beat will be measured with the sticky patches attached to your chest.</i> ”	REQUIRED (only for Sites Participating in HRV component of the Vascular Tests Sub-Study)
Page 3-4	Revised language. DELETED: “Your pulse will then be measured with a sensor placed on your wrist and upper leg. This test gives doctors information about the stiffness or flexibility of your arteries.”	REQUIRED (only for Sites Participating in any component of the Vascular Tests Sub-Study)
Page 4	ADDED “... <<OMIT OR DELETE VASCULAR TEST IF TESTING DOES NOT APPLY TO YOUR SITE>> <i>Vascular Tests, ...</i> ”	REQUIRED (only for Sites Participating in any component of the Vascular Tests Sub-Study)
Page 4	ADDED “... <i>cardiac MRI</i> ...”	REQUIRED
Page 5	Revised blood volume and visit number. ADDEDD “If all <i>15</i> study visits ...” DELETED “... 16 to 26 ...” ADDED “ <i>26 to 44</i> ” DELETED “..., 3, 4, , 5, 6, 7, 8 and 9 ...” ADDED “... <i>through 14</i> ...”	REQUIRED
Page 7	Protocol change risk of test to be done as a sub-study. DELETED: “ <u>Pulse Wave Velocity</u> ” ADDED: “ <u><i>Vascular Tests</i></u> ”	REQUIRED (only for Sites Participating in any component of the Vascular Tests Sub-Study)
Page 8	Revised language, ADDED “ <i>or other continued follow-up</i> ”	REQUIRED
Page 12	Revised timeline, DELETED “Pulse Wave Velocity” ADDED “ <i>Vascular Tests</i> ” ADDED “ <i>Visits 11 – 14</i> ”	REQUIRED

26.9 CONSENT FORM AMENDMENT: June 1, 2014

The Consent Form Table below lists the changes made to the June 1, 2014 version of the Consent Form Template. You may need to change the page numbers in the table below to match the page numbers in your IRB approved consent form **All changes to original text will be printed in bold italics*. Recommended changes are only suggestions and do not have to be incorporated into your consent form.

Page # on the 6/1/14 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Change / RATIONALE FOR CHANGE																																	
All pages, except pages 5 & 6	Throughout the document formatting changes were made to the instructions to insert or omit language and phrases. Additional changes were made to font style and font size.	ADMINISTRATIVE CHANGE: To standardize CKiD consent forms.																																	
Page 1	Updated the Version Date of the Consent to 6/1/14	REQUIRED CHANGE RATIONALE: To specify the latest Version of the CKiD Consent Form.																																	
Page 1	Updated the number of enrolled subjects in the following statement: About 900 children between the ages of 1 and 16 years...	REQUIRED CHANGE RATIONALE: To accurately reflect the number of enrolled subjects in the study.																																	
Page 1	Updated the following sentence: “...(before 17 th birthday) at the time of enrollment , with ...	REQUIRED CHANGE RATIONALE: To accurately reflect the age of subjects at enrollment.																																	
Page 2	Updated the number of visits possible in the following statement: “Attend up to 16 study visits.”	REQUIRED CHANGE RATIONALE: Number of visits increased to include the possibility of an irregular visit.																																	
Page 2	<p>FOR EXAMPLE, IF YOUR SITE ENROLLED A CHILD IN 2005, THEN THIS PARTICIPANT MAY COMPLETE UP TO 16 STUDY VISITS. HOWEVER, IF A CHILD ENROLLED IN 2006, THEN THE NUMBER OF POTENTIAL STUDY VISITS IS UP TO 15. REFER TO THE TABLE BELOW FOR FURTHER ILLUSTRATION. THIS TABLE DOES NOT NEED TO BE INCLUDED IN YOUR CONSENT FORM>></p> <table border="1" data-bbox="478 1049 1432 1393"> <thead> <tr> <th><i>Year of Enrollment (i.e. Completed Visit 1A)</i></th> <th><i>Potential number of study visits completed by 2018</i></th> <th><i>Potential visit number completed by 2018</i></th> </tr> </thead> <tbody> <tr><td>2005</td><td>16 (including irregular visit)</td><td>Visit 15</td></tr> <tr><td>2006</td><td>15 (including irregular visit)</td><td>Visit 14</td></tr> <tr><td>2007</td><td>14 (including irregular visit)</td><td>Visit 13</td></tr> <tr><td>2008</td><td>13 (including irregular visit)</td><td>Visit 12</td></tr> <tr><td>2009</td><td>12 (including irregular visit)</td><td>Visit 11</td></tr> <tr><td>2010</td><td>11 (including irregular visit)</td><td>Visit 10</td></tr> <tr><td>2011</td><td>10 (including irregular visit)</td><td>Visit 9</td></tr> <tr><td>2012</td><td>9 (including irregular visit)</td><td>Visit 8</td></tr> <tr><td>2013</td><td>8 (including irregular visit)</td><td>Visit 7</td></tr> <tr><td>2014</td><td>7 (including irregular visit)</td><td>Visit 6</td></tr> </tbody> </table>	<i>Year of Enrollment (i.e. Completed Visit 1A)</i>	<i>Potential number of study visits completed by 2018</i>	<i>Potential visit number completed by 2018</i>	2005	16 (including irregular visit)	Visit 15	2006	15 (including irregular visit)	Visit 14	2007	14 (including irregular visit)	Visit 13	2008	13 (including irregular visit)	Visit 12	2009	12 (including irregular visit)	Visit 11	2010	11 (including irregular visit)	Visit 10	2011	10 (including irregular visit)	Visit 9	2012	9 (including irregular visit)	Visit 8	2013	8 (including irregular visit)	Visit 7	2014	7 (including irregular visit)	Visit 6	OPTIONAL CHANGE RATIONALE: Instruction describing the maximum number of visits which may occur at your site. Number of potential visits is based on when subject was enrolled in study. Table added to clarify the number of visits possible.
<i>Year of Enrollment (i.e. Completed Visit 1A)</i>	<i>Potential number of study visits completed by 2018</i>	<i>Potential visit number completed by 2018</i>																																	
2005	16 (including irregular visit)	Visit 15																																	
2006	15 (including irregular visit)	Visit 14																																	
2007	14 (including irregular visit)	Visit 13																																	
2008	13 (including irregular visit)	Visit 12																																	
2009	12 (including irregular visit)	Visit 11																																	
2010	11 (including irregular visit)	Visit 10																																	
2011	10 (including irregular visit)	Visit 9																																	
2012	9 (including irregular visit)	Visit 8																																	
2013	8 (including irregular visit)	Visit 7																																	
2014	7 (including irregular visit)	Visit 6																																	

Page 3	As a part of this continued follow-up we will also <i>look at your child's medical</i> record (deleted "your child's") <i>for their</i> most recent laboratory results, <i>medical treatments, and measurements such as height, weight and blood pressure</i> .	RECOMMENDED CHANGE RATIONALE: Clarification of the medical information that will be recorded for the Continued Follow Up.
Page 3	Some of these instruments will be directly administered to your child by a trained professional (deleted "and") <i>at visits 1B, 3, 5 and 7</i> . (Deleted "some of these") Moved the phrase " <i>The behavior (questionnaires) instruments will be given to you to complete on your own starting at visit 1B and every two years after that.</i> ") You will (deleted "also") be informed, through your nephrologist, if your child's answers suggest the possibility of self-injury or injury to others.	REQUIRED CHANGE RATIONALE: To document the Steering Committee decision to discontinue neurocognitive assessments at V9.
Page 3	Every (deleted "other") <i>two</i> years beginning with V2, we will use an Ambulatory Blood Pressure Monitor (ABPM) to look for abnormal patterns of blood pressure over the day and night.	RECOMMENDED CHANGE RATIONALE: Grammatical change to simplify statement regarding frequency of ABPM.
Page 4	Every (deleted "other") <i>four</i> years beginning with the V2 an echocardiogram (ECHO) will be done.	REQUIRED CHANGE RATIONALE: To document Steering Committee decision to perform ECHO at visits V2, V6, V10, and V14.
Page 4	Updated sentence: In some children, we will also take a picture with ultrasound of the carotid arteries (<i>C-IMT</i> , blood vessels that run through the neck).	RECOMMENDED CHANGE RATIONALE: To clarify that ultrasound of carotid arteries is the same as C-IMT
Page 4	<i>Every two years</i> (deleted "S") starting at V2, we will perform vascular tests to determine whether stiffer arteries put patients at risk for heart or kidney problems in the future.	RECOMMENDED CHANGE RATIONALE: Grammatical change to simplify statement regarding frequency of vascular tests.
Page 4	Updated sentence: The picture will allow us to check <i>for</i> coronary heart disease and <i>other</i> conditions.	RECOMMENDED CHANGE RATIONALE: Grammatical change
Page 4	If the ECHO, <i>Only include "Vascular Tests" if applicable to your site</i> Vascular Tests, <i>Only include "C-IMT" if applicable to your site C-IMT</i> , Ambulatory Blood Pressure Monitoring (ABPM)...	RECOMMENDED CHANGE RATIONALE: For clarification purposes
Page 5	Updated the number of visits possible and amount of blood collected in the following statements: If all <i>16</i> (deleted 5) study visits are completed, the amount of extra blood will be about <i>28</i> (deleted "6") to <i>47</i> (deleted "4") teaspoons over the entire study depending upon your child's weight. The total amount of blood for Study Visit 1B, 2 through <i>15</i> (deleted "4") including the Biological Sample will be approximately 3 to 6 teaspoons per visit depending on	REQUIRED CHANGE RATIONALE: Number of visits increased to include the possibility of an irregular visit. Also updated the total amount of blood to be collected allowing for an irregular visit.

	your child's weight.	
Page 6	<i>If you choose to participate in this optional part of the study, genetic testing will be done on your child's blood sample. Genetic testing looks at pieces of DNA called genes, which contain the information needed to build and operate the human body.</i>	RECOMMENDED CHANGE RATIONALE: Additional clarification of definition of genetic testing.
Page 6	<i>These samples and test results may be shared with other researchers and scientists. However, they will not know who you are as they will only receive the sample with a coded number without any of your identifying information. It will not be possible to share any test results with you or your doctors because the samples and test results will be coded.</i>	REQUIRED CHANGE RATIONALE: Additional statement to clarify genetic sample is de-identified, may be shared with outside investigators, and no results will be reported.
Page 6 - 7	<p>Addition of language explaining Optional consent to link information from public health databases with instructions: <i>OPTIONAL Consent for Use of Data for Future Research</i> <i>To further help us understand what happens to people who have CKD for many years, we may want to obtain information about your health status in the future. Public health databases supported by the government (such as the Census, Unites States Renal Data System [USRDS], Scientific Registry of Transplant Recipients [SRTR], <<CANADIAN SITES SHOULD LIST the Canadian Organ Replacement Register [CORR] instead of the Census, USRDS, or SRTR>>) may provide the CKiD study with valuable information in the years to come about your health and medical treatments such as dialysis and transplant.</i></p> <p><i>National databases collect and file information by social security number <<CANADIAN SITES SHOULD LIST THE PROVINCIAL HEALTH ID INSTEAD OF SSN>> and by name and date of birth. With your permission, the CKiD study would like to periodically check if there is health related information on file about you in a public health database. As the social security number is the most accurate way and preferred method of linking this information, we would like your permission to use your social security number. <<CANADIAN SITES SHOULD LIST THE PROVINCIAL HEALTH ID INSTEAD OF</i></p>	REQUIRED CHANGE RATIONALE: To document the Steering committee decision to obtain health status information from public databases such as USRDS, SRTR, NDI, and CORR.

	<p>SSN>> However, if you prefer, we can use your name and date of birth instead.</p> <p>Insert Clinical Site Name will provide the public health databases with a coded CKiD study identification number along with your social security number <<CANADIAN SITES SHOULD LIST THE PROVINCIAL HEALTH ID INSTEAD OF SSN>> or name and date of birth. To help protect your privacy, information provided to the CKiD study from the national database will only be identified by the coded CKiD study identification number. There are no public records that could link the CKiD study identification number to your personal information. This process will keep your social security number and name separate from any medical study information that the CKiD study has on record.</p> <p>Your information will only be available to researchers who are specifically approved to do these studies. You can change your mind about participating in this optional part of the study at any time. If at a later date you decide you no longer want to participate, information that has already been collected will be kept, however, no further information about you will be collected. You can still participate in the rest of this study even if you do not want to participate in this portion. Please indicate whether you are willing to allow the researchers to use your personal information for this future research by marking YES or NO and providing your initials and the date next to each choice below:</p> <p>MY CHILD’S SOCIAL SECURITY NUMBER MAY BE USED TO LINK PUBLIC HEALTH DATABASE INFORMATION FOR USE IN THE CKiD STUDY.</p> <p>YES <input type="checkbox"/> NO <input type="checkbox"/> Initials _____ Date _____</p> <p>MY CHILD’S NAME AND DATE OF BIRTH MAY BE USED TO LINK PUBLIC HEALTH DATABASE INFORMATION FOR USE IN THE CKiD STUDY.</p> <p>YES <input type="checkbox"/> NO <input type="checkbox"/> Initials _____ Date _____</p>	
Page 8	<p><u>Echocardiogram</u> Only include “C-IMT” if this testing is done at your site and C-IMT: There are no confirmed side effects from present diagnostic ultrasound instruments (echocardiogram Only include “C-IMT” if this testing is done at your site and C-IMT)</p>	RECOMMENDED CHANGE: For clarification and grammatical change

Page 9	<i>If you have a cardiac MRI done, you will receive an additional \$25.</i>	RECOMMENDED CHANGE RATIONALE: Suggestion of Steering Committee to provide compensation for completion of MRI.
Page 9	Holiday cards, (deleted “or”) <i>birthday cards or thank you cards</i> may be given to the families (deleted “at the holidays”) as a token of appreciation for their participation.	RECOMMENDED CHANGE RATIONALE: To clarify what may be received as a study participant in the CKiD study. Recommendation was based on “best practices” for retention of subject in study.
Page 10	They may collect other information including your name, address, date of birth, (added “social security number”) and other details.	RECOMMENDED RATIONALE: To clarify that social security numbers may be part of the personal information recorded and used for this study.
Page 13	Changes made to CKiD Study Timetable	REQUIRED CHANGE RATIONALE: To document Steering Committee decision to change frequency of tests.

26.10 CONSENT FORM AMENDMENT: June 1, 2016

The Consent Form Table below lists the changes made to the June 1, 2016 version of the Consent Form Template. You may need to change the page numbers in the table below to match the page numbers in your IRB approved consent form **All changes to original text will be printed in bold italics*. Recommended or Optional changes are only suggestions and do not have to be incorporated into your consent form.

Page # on the 6/1/16 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Change / RATIONALE FOR CHANGE
Page 1	Updated the Version Date of the Consent to <i>6/1/16</i>	REQUIRED CHANGE RATIONALE: To specify the latest version of the CKiD Consent Form.
Page 1	“The word “you” in this consent form will refer to both you and your child <i>unless specified</i> ”	OPTIONAL CHANGE RATIONALE: To clarify language in consent form. Changes throughout document are made for language consistent with a parental/legal guardian consent form.
Page 1	“About <i>1080</i> (deleted “900”) children between the ages of <i>6 months</i> (deleted “1 year”) and 16 years... with (deleted “mild to moderate”) CKD...”	REQUIRED CHANGE RATIONALE: To update the target enrollment numbers and age criteria for Cohort 3 enrollment.
Page 2	“You (deleted “and your child”) will be given instructions prior...”	OPTIONAL CHANGE RATIONALE: Stated previously that “The word “you” in this consent form will refer to both you and your child <i>unless specified</i> ”
Page 2	“...instructions prior to each study visit which (deleted “will”) <i>may</i> include a study...”	RECOMMENDED CHANGE RATIONALE: Clarification that not all materials listed may be needed before a visit for every participant.
Page 2	“...for example, (deleted “your child’s birth weight which is”) information that you may need to look up at home (<i>such as your child’s birth weight</i>), ...”	OPTIONAL CHANGE RATIONALE: Simplified phrasing for easier reading level.

Page 2	“...and a copy of some of the forms for you (deleted “and your child”) to complete...”	OPTIONAL CHANGE RATIONALE: Stated previously that “The word “you” in this consent form will refer to both you and your child <i>unless specified</i> ”												
Page 2	<table border="1"> <thead> <tr> <th><i>Year of Enrollment (i.e. Completed Visit 1A)</i></th> <th><i>Potential number of study visits completed by 2018</i></th> <th><i>Potential visit number completed by 2018</i></th> </tr> </thead> <tbody> <tr> <td><i>2016</i></td> <td><i>3</i></td> <td><i>Visit V2</i></td> </tr> <tr> <td><i>2017</i></td> <td><i>3</i></td> <td><i>Visit V2</i></td> </tr> <tr> <td><i>2018</i></td> <td><i>2</i></td> <td><i>Visit V1B</i></td> </tr> </tbody> </table>	<i>Year of Enrollment (i.e. Completed Visit 1A)</i>	<i>Potential number of study visits completed by 2018</i>	<i>Potential visit number completed by 2018</i>	<i>2016</i>	<i>3</i>	<i>Visit V2</i>	<i>2017</i>	<i>3</i>	<i>Visit V2</i>	<i>2018</i>	<i>2</i>	<i>Visit V1B</i>	REQUIRED CHANGE (if using this table) RATIONALE: Added potential number of visits completed by 2018 for new participants.
<i>Year of Enrollment (i.e. Completed Visit 1A)</i>	<i>Potential number of study visits completed by 2018</i>	<i>Potential visit number completed by 2018</i>												
<i>2016</i>	<i>3</i>	<i>Visit V2</i>												
<i>2017</i>	<i>3</i>	<i>Visit V2</i>												
<i>2018</i>	<i>2</i>	<i>Visit V1B</i>												
Page 2	“Each participant will be in this study for about <i>one</i> (deleted “five (5)”) to 13 years.”	REQUIRED CHANGE RATIONALE: To clarify the number of years of participation for new participants.												
Page 2	“(Deleted “ <i>The length of the s</i> ”) Study visits will take (deleted “are as follows; (V1A, V2, V4, V6, V8...etc) about 7 hours; Visit 1B (V1B, V3, V5, V7, V9...etc)”) about 4 hours to complete. ”	REQUIRED CHANGE RATIONALE: 2016 amendment changes which discontinue the iohexol GFR (iGFR) test for majority of participants will result in shorter visits. Most visits now will take about 4 hours.												
Page 2 - 3	“For children (deleted “1”) 6 months to 3 years of age Study Visit 1B (deleted “the second visit”) will occur within 3 months of the first visit. ...”	REQUIRED CHANGE RATIONALE: Clarified the age of participants based on new inclusion criteria. Simplified phrasing for easier reading level is optional.												
Page 3	“(Deleted “We may ask to measure your child’s kidney function at this visit, if it has been more than 3 months since their last measurement in the study. Afterwards, If you are unable to attend future study visits w”) We would continue follow up with you on a yearly basis. This <i>continued</i> follow-up would be an interview that may be completed via phone, <i>by mail</i> , in-person interview or on-line survey.”	REQUIRED CHANGE RATIONALE: Per June 2016 Amendment, the iGFR test will no longer be completed at irregular visit. Changes in phrasing for easier understanding and clarification optional.												
Page 3	“Participate in the (deleted “F”) <i>f</i> ollowing (deleted “S”) <i>s</i> tudy (deleted “P”) <i>p</i> rocedures:”	OPTIONAL CHANGE RATIONALE: With reformatting it is not necessary to capitalize words in this heading.												
Page 3	“ <i>All children participating in the study will have</i> (deleted “B”) <i>b</i> lood and urine tests <i>done</i> (such as Creatinine) (deleted “will also be done”) to measure kidney function at (deleted “each study visit.”) <i>every visit except for the V1b.</i> ”	RECOMMENDED CHANGE RATIONALE: Moved sentence to top of “To study kidney function” section as it applies to all participants. Clarification that creatinine is not measured at the V1B visit.												

Page 3	<p><i>“In addition, some children may have an iohexol GFR (iGFR) test completed at Visits 1A, V2, V4, V6, V8, V10, V12 and V14. An iGFR test is a</i> (deleted “A”) very accurate measurement of (deleted “your child’s”)-kidney function and level of CKD (deleted “will be used”). This test measures (deleted “your child’s”)-Glomerular Filtration Rate (GFR). <i>A visit with an iGFR test will last about 7 hours. If you joined the study before 2014, and your child’s last iGFR measurement was 90 or higher, your child will be asked to complete the iohexol test. If you are joining the study after 2015, the iGFR test is optional and you can choose not to have the test done.</i></p> <p><i>When the iGFR test is to be completed,</i> (deleted “Y”) your child will come to...”</p>	<p>REQUIRED CHANGE RATIONALE: Per the June 2016 amendment, only some participants will undergo an iGFR test. Included the criteria used to determine which participants may undergo the test and how long the visits will take.</p>
Page 3	<p>“The behavior (deleted “(”) questionnaires (deleted “) instruments”) will be...”</p> <p>“You will be informed, through your nephrologist, if your (deleted “child’s”) answers suggest the possibility <i>that your child is at risk for</i> self-injury or injury to others.”</p> <p>“Neurocognitive testing (deleted” data”) cannot be (deleted “obtained”)-<i>completed</i> during the (deleted “child’s”) scheduled study visit, it (deleted “these measurements”) should be <i>done</i> within (deleted “+/- ”) one month.”</p>	<p>OPTIONAL CHANGE RATIONALE: To simplify phrasing and make the language consistent with a parental/legal guardian consent form.</p>
Page 4	<p>“We will also take blood pressure the way you usually (deleted “get it”) <i>have it measured</i> in clinic.”</p> <p>The ECHO uses ultrasound to take pictures of (deleted “your child’s”) the heart.</p>	<p>OPTIONAL CHANGE RATIONALE: Simplified language for easier reading.</p>
Page 4	<p>“(Deleted “In some “) <i>Also, for</i> children <i>who are 5 years of age and older</i> we will (deleted “also”) take a picture (deleted “with ultrasound”) of <i>the blood vessels that run through the neck</i> (carotid arteries) <i>using</i> (deleted “(”) <i>ultrasound</i> (C-IMT (deleted” blood vessels that run through the neck”)).</p> <p>...”</p>	<p>REQUIRED CHANGE (for sites performing the C-IMT) RATIONALE: To clarify the age range of participants for whom C-IMTs should be performed. Also simplified the phrasing for easier reading level.</p>
Page 4	<p><i>“For children who are 5 years old and older, we will perform vascular tests</i> (deleted “E”) every two years starting at V2 (deleted “;”). <i>These tests will help us</i> (deleted “we will perform vascular tests to”) determine whether stiffer arteries put patients at risk for heart or kidney problems in the future.”</p>	<p>REQUIRED CHANGE –only for sites performing vascular tests RATIONALE: To clarify the age range of participants for whom vascular tests should be performed. Also simplified phrasing for easier reading level suggested.</p>

Page 4	<p>Simplified language regarding vascular test:</p> <p>“...information about the stiffness or flexibility of (deleted “your”) arteries.”</p> <p>“During this non-invasive procedure, (deleted “you”) <i>your child</i> will have sticky patches placed on (deleted “your”) <i>their</i> chest and a small instrument shaped like a pen will be placed on (deleted “your”) the wrist to record the heart beat.”</p> <p>“Then the same pen-shaped instrument will be placed on the side of your <i>child’s</i> neck and the top of <i>the</i> (deleted “your”) leg to measure the speed of <i>their</i> (deleted “your”) pulse.”</p> <p>“Additionally, (deleted “you”) <i>your child</i> will lie still for 10 more minutes and (deleted “your”) <i>their</i> heart beat will be measured...”</p> <p>“...heart beat will be measured (deleted “with the sticky patches attached to your chest”).”</p>	<p>OPTIONAL CHANGE RATIONALE: To simplify the description of vascular tests and make language consistent with a parental/legal guardian consent form.</p>
Page 5	<p>“You (deleted “These children”) will be asked to complete a questionnaire to ensure (deleted “they are “) <i>your child is</i> eligible to have a cardiac MRI performed.”</p> <p>“...magnets and computers to take a picture of (deleted “your child’s”) <i>the</i> heart.”</p> <p>“...MRI cannot be obtained during the child’s scheduled study visit, (deleted “these measurements”) <i>they</i> should be (deleted “scheduled”)-<i>completed</i> within (deleted “+/-”) one month (deleted “of the scheduled visit”).</p>	<p>OPTIONAL CHANGE RATIONALE: To simplify the phrasing and make language consistent with a parental/legal guardian consent form.</p>
Page 5	<p>“(deleted “At every other visit beginning at the V3 visit we will do a 6 minute walk test (6MWT) which is used to measure how far your child can walk in 6 minutes. The 6MWT is done indoors in an appropriate corridor using cones to mark distance.”)</p>	<p>REQUIRED CHANGE RATIONALE: June 2016 Amendment includes cessation of 6 minute walk test from protocol. Communication Memo 227 announced the Steering Committee’s decision to discontinue this procedure however the protocol would be revised at a later time. NOTE: This consent form change may have already been submitted to your IRB.</p>
Page 5	<p>“Your child’s doctor will give a brief physical exam at every study visit <i>except for the second visit (Visit 1B).</i>”</p>	<p>RECOMMENDED CHANGE RATIONALE: To clarify which visits the doctor will perform the exams for the study.</p>

Page 5	<p>“We will ask you (deleted “and your child”) to complete several forms.”</p> <p>“...health care resources you (deleted “and your child”) use”</p> <p>“...any time <i>your child spent</i> in the hospital (deleted “your child spent”)-since the last study visit.”</p> <p>“We may also collect information from your <i>child’s</i> medical record.”</p> <p>“Information collected will include the following: (deleted “your”)-diagnosis, lab results...”</p>	<p>OPTIONAL Change RATIONALE: To simplify the phrasing and make language consistent with a parental/legal guardian consent form.</p>
Page 5 - 6	<p><i>“Tests related to kidney health and function (such as kidney ultrasounds or ambulatory blood pressure monitoring reports) may be reviewed by a researcher selected by the CKiD study. This may be a physician outside of Insert Clinical Site Name.”</i></p>	<p>REQUIRED CHANGE RATIONALE: To clarify that some health information obtained from the participant’s medical record chart may be sent to and reviewed by a CKiD study researcher and or physician outside of the participant’s CKiD site.</p>
Page 6	<p>“Receive (deleted “T”) <i>t</i>est (deleted “R”) <i>r</i>esults”</p>	<p>OPTIONAL Change RATIONALE: With reformatting it is not necessary to capitalize words in heading.</p>
Page 6	<p>“You will receive the results of the Iohexol GFR test (<i>if completed</i>)...”</p>	<p>REQUIRED CHANGE RATIONALE: To clarify that only participants that have an iohexol GFR test performed will receive these results.</p>
Page 6	<p>“If you want, the results of your <i>child’s</i> tests will...”</p>	<p>OPTIONAL CHANGE RATIONALE: To make language consistent with a parental/legal guardian consent form.</p>
Page 6	<p>“Donate OPTIONAL (deleted “optional”) biological and genetic samples.”</p>	<p>OPTIONAL Change RATIONALE: Reformatting to capitalize important word in this heading.</p>
	<p>“at each study visit beginning with the V1B...”</p> <p>“...Repository from each study visit beginning with the V1B.”</p> <p>“...the nail clippings and hair samples are not collected at V1B (deleted “b”),...”</p> <p>“...total amount of blood for Study Visit 1B (deleted “, 2”) through 15</p>	<p>OPTIONAL CHANGE RATIONALE: Minor edits so name of visit consistent throughout document.</p>

Page 6	“...depending on your child’s weight <i>and if your child will have an iohexol GFR completed.</i> ”	RECOMMENDED CHANGE RATIONALE: Total blood volume collected will be slightly less for participants not having the iohexol test.
Page 6	“...they will destroy your <i>child’s</i> (deleted “sample and all information that identifies him/her”).	OPTIONAL Change RATIONALE: Redundant wording as the repository does not collect any personal identifiers.
Page 7	<i>“Your child’s sample will be stored in a way that allows cells to grow and multiply. These multiplying cells may give rise to what is called a cell line. Cell lines may be kept alive indefinitely or for many years and can be used for many different studies in the future. Some future studies may include looking at a complete set of DNA to look for variations in genes.”</i>	RECOMMENDED CHANGE RATIONALE: Additional information to clarify how genetic sample is stored and used.
Page 7	“However, they will not know who (deleted “you are”) <i>your child is</i> as they will only receive the sample with a coded number without any (deleted “of your”) <i>personal</i> identifying information.”...	OPTIONAL Change RATIONALE: To make language consistent with a parental/legal guardian consent form.
Page 7	<i>OPTIONAL sharing of information for ongoing research</i> “...about your <i>child’s</i> health status in the future.” “...information in the years to come about your <i>child’s</i> health and medical treatments...”	OPTIONAL Change RATIONALE: New heading for optional data linking and to make language consistent with a parental/legal guardian consent form.
Page 7 - 8	“...by social security number, <<CANADIAN SITES SHOULD LIST THE PROVINCIAL HEALTH ID INSTEAD OF SSN>> (deleted “and by”)-name, (deleted “and”) date of birth, <i>and gender.</i> ”	REQUIRED CHANGE RATIONALE: June 2016 amendment specifies that additional identifiers are required for data linking.
Page 8	“...on file about (deleted “you”) <i>your child</i> in a public health database (deleted “.”) <i>by using your child’s personal identifiers to request health information.</i> ” (Deleted “As the social security number is the most accurate way and preferred method of linking this information, we would like your permission to use your social security number. <<CANADIAN SITES SHOULD LIST THE PROVINCIAL HEALTH ID INSTRED OF SSN>>”) (Deleted “However if you prefer we can use your name and date of birth instead.”)	REQUIRED CHANGE RATIONALE: June 2016 amendment defines personal identifiers to include more than social security number/ Provincial Health ID. Language made consistent with a parental/legal guardian consent form is optional.

Page 8	<p><i>“In order to protect your child’s identity, a third party called an honest broker will be used. By using the honest Broker, the CKiD study will not receive any of your child’s personal identifiers. The Children’s Hospital of Philadelphia Research Institute will be the honest broker for this study.”</i></p>	<p>REQUIRED CHANGE RATIONALE: To explain the identity and role of an honest broker used for the data linking with public health databases.</p>
Page 8	<p><i>“With your permission,</i></p> <ul style="list-style-type: none"> • <i>Insert Clinical Site Name</i> will provide the (deleted “public health”) <i>databases honest broker</i> with a (deleted “coded”) CKiD study identification number along with your <i>child’s</i> social security number <<CANADIAN SITES SHOULD LIST THE PROVINCIAL HEALTH ID INSTEAD OF SSN>>, (deleted “or”) name, (deleted “and”) date of birth, <i>and gender</i>. • <i>The honest broker will provide the personal identifiers to the databases along with a coded number that is different from the CKiD study identification number.</i> • <i>The databases will provide health information to the honest broker with only the coded number attached.</i> • <i>The honest broker will replace the coded number with the CKiD identification number and send the health information to the CKiD study’s Data Coordinating Center.</i> (Deleted “To help protect your privacy, information provided to the CKiD study from the national database will only be identified by the coded CKiD study identification number.”) 	<p>REQUIRED CHANGE RATIONALE: To document the establishment of the Honest Broker and to clarify that all four personal identifiers will be used to request health related information from the National Databases.</p> <p>Made language consistent with a parental/legal guardian consent form is optional.</p>
Page 8	<p>Clarification of language for parental/guardian consent for data link:</p> <p>“There are no public records that could link the CKiD study identification number to your <i>child’s</i> personal information.”</p> <p>“This process will keep your <i>child’s</i> social security number...”</p> <p>“Your <i>child’s</i> information...”</p> <p>“...no further information about your <i>child...</i>”</p> <p>“...willing to allow the researchers to use your <i>child’s</i> personal information.”</p>	<p>OPTIONAL CHANGE RATIONALE: To make language consistent with parental/legal guardian consent.</p>

Page 8	<p>“...marking YES or NO and providing your initials and the date (delete “next to each choice”) below:</p>	<p>RECOMMENDED CHANGE RATIONALE: Simplified instructions for easier understanding.</p>
Page 8	<p><i>MY CHILD’S SOCIAL SECURITY NUMBER, NAME, DATE OF BIRTH, AND GENDER MAY BE USED TO LINK PUBLIC HEALTH DATABASE INFORMATION FOR USE IN THE CKiD STUDY.</i></p> <p>(Delete “MY CHILD’S SOCIAL SECURITY NUMBER MAY BE USED TO LINK PUBLIC HEALTH DATABASE INFORMATION FOR USED IN THE CKiD STUDY”)</p> <p>(Delete “MY CHILD’S NAME AND DATE OF BIRTH MAY BE USED TO LINK PUBLIC HEALTH DATABASE INFORMATION FOR USED IN THE CKiD STUDY”)</p>	<p>REQUIRED CHANGE RATIONALE: June 2016 amendment introduced option for families to share information with other studies. This will reduce burden on participants as they will not have to undergo duplicate procedures and completion of questionnaires in cases where similar data is being obtained by different studies.</p>
Page 8	<p><i>“Consent for Sharing of Data Between Research Studies</i></p> <p><i>If you enroll in another research study at <u>Insert Clinical Site Name</u>, some procedures and questionnaires may be done in both studies. This may include lab test results, medical history or other information about you/your child such as age, race, education, and household income. In this case, information collected in one study may be shared with the other, so you will not have to repeat it again. This information will only be shared if you agree to participate in both studies. You can change your mind about participating in this optional part of the study at any time. Please indicate whether you are willing to allow the researchers to share your child’s information at <u>Insert Clinical Site Name</u> by marking YES or NO and providing your initials and the date.</i></p> <p><i>INFORMATION OBTAINED BY THE CKiD STUDY MAY BE SHARED WITH ANOTHER STUDY PERFORMED AT <u>Insert Clinical Site Name</u>.</i></p> <p>YES <input type="checkbox"/> NO <input type="checkbox"/> Initials _____ Date _____</p>	<p>REQUIRED CHANGE RATIONALE: June 2016 amendment introduced option for families to share information with other studies.</p>

Page 8	<p><i>OPTIONAL Consent for the iGFR Test (Only for study participants joining the study after 2015)</i> <i>If you join the study after 2015 you can choose whether or not to have an iohexol GFR test performed at Visits 1A, V2, V4, V6, V8, V10, V12 and V14. The test is described in detail on page 3 of this consent form. You can change your mind about participating in this optional part of the study at any time. You can still participate in the rest of this study even if you do not want to participate in this portion. Please indicate whether you are willing to have iGFR testing by marking YES, or NO.</i></p> <p><i>I AGREE TO HAVE THE IOHEOXL TEST DONE AS A PART OF THE STUDY</i></p> <p><i>YES <input type="checkbox"/> NO <input type="checkbox"/> Initials _____ Date _____</i></p>	<p>REQUIRED CHANGE RATIONALE: June 2016 amendment introduced option for newly enrolled participants to have an iohexol GFR test performed. Participants can indicate separately which option they choose.</p>
Page 9	<p>“Prior to (delete “your”) the exam, you will be asked to complete a standard questionnaire.”</p> <p>“The purpose of this questionnaire is to ensure <i>that it is safe to</i> (delete “you are able to safely”) enter the MRI area”</p> <p>“important to ensure your <i>child</i> will be safe”</p>	<p>OPTIONAL CHANGE RATIONALE: Language made consistent with parental/legal guardian consent.</p>
Page 9	<p>(delete “6 Minute Walk Test There are no confirmed side effects from participating in this test.”)</p>	<p>REQUIRED CHANGE RATIONALE: No longer performing test.</p>
Page 10	<p>“... but could participate in <i>the continued</i> (PIP) follow- up interviews <i>or on-line surveys.</i>”</p>	<p>RECOMMENDED CHANGE RATIONALE: To clarify all methods used by the study that are available for continued follow up.</p>
Page 10	<p>“...Therefore, you (delete “and your child”) will have more...”</p>	<p>OPTIONAL CHANGE RATIONALE: Language made consistent with parental/legal guardian consent.</p>

<p>Page 10 - 11</p>	<p>“\$100 (delete “\$150”) <i>for each study visit completed (Visit 1A through VI)</i> (delete “V2, V4, V6, V8...etc.”)</p> <p><i>“An additional \$50 for completion of an iohexol test at Study Visit (1A, V2, V4, V6, V8... etc.)”</i></p> <p><i>“An additional \$50 for completion of</i> (delete “If you have”) a cardiac MRI (delete “done, you will receive an additional \$25”).</p> <p><i>“If you need to return to the clinic on a second day to complete an ECHO, ABPM, or cognitive test, you will receive an additional \$25.”</i></p> <p>(Delete “75 for completion of each Study Visit (1B, V3, V5, V7, V9... etc.).”</p> <p>“(Delete “We will give you”) \$50 for each (delete “Phone /In Person Follow up (PIP) or other”) continued follow-up (PIP) interview, <i>or on-line survey</i> completed.”</p>	<p>RECOMMENDED CHANGE Note: Each site must determine the amount appropriate for participant compensation, and what your local budget may allow. The amounts listed here are merely suggestions. If your site chooses to decrease the patient compensation, you may consider using the following rationale.</p> <p>RATIONALE: Compensation amounts for Visits 1A, V2, V4, V6, V8, etc were reduced as the visits will be shorter without an iohexol GFR test. Phrasing simplified and optional.</p>
<p>Page 11</p>	<p>“(Delete “You”) <i>Your child</i> needs treatment not allowed in this study.”</p> <p>“(Delete “You”) <i>Your child</i> becomes pregnant. <i>You child would not be allowed to continue with study visits, but can participate in the continued follow-up interviews or online survey.</i>”</p> <p>“There may be other reasons to take (Delete “you”) <i>your child</i> out of the study that we do not know at this time.”</p>	<p>OPTIONAL CHANGE RATIONALE: Language made consistent with parental/legal guardian consent. Added clarification that pregnant study subjects can continue participating in the study.</p>
<p>Page 12</p>	<p><i>“If you gave permission on page X, the Honest Broker located at Children’s Hospital of Philadelphia, and public health databases such as the Census, United States Renal Data System, and the Scientific Registry of Transplant Recipients may receive your personal information.”</i></p>	<p>REQUIRED CHANGE RATIONALE: June 2016 amendment specifies who will serve as the honest broker. Was included to this section as additional people outside of the local site who may see the participant’s information.</p>
<p>Page 16</p>	<p><i>Updated CKiD Time Table</i></p>	<p>REQUIRED CHANGE RATIONALE: Reflects test changes per June 2016 amendment.</p>

26.11 CONSENT FORM AMENDMENT: August 1, 2017

The Consent Form Table below lists the changes made to the August 1, 2017 version of the Consent Form Template. You may need to change the page numbers in the table below to match the page numbers in your IRB approved consent form **All changes to original text will be printed in bold italics*. Recommended or Optional changes are only suggestions and do not have to be incorporated into your consent form.

Page # on the 8/1/17 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Change / RATIONALE FOR CHANGE
Page 1	Updated the Version Date of the Consent to <i>“8/1/17”</i>	REQUIRED CHANGE RATIONALE: To specify the latest version of the CKiD Consent Form.
Page 2	Moved paragraph: “About 1080 children between the ages of 6 months and 16 years (before 17 th birthday) at time of enrollment, with CKD, and from <i>about</i> 50 different places around North America will be in this study. About <i>Insert Project Number</i> children will be asked to be in this study at <i>Insert Clinical Site Name.</i> ” to heading # 4.	RECOMMENDED CHANGE RATIONALE: This paragraph describes how many participants will be in the study (heading # 4). Added word to reflect exact number of study sites may vary slightly.
Page 2	Deleted “If you have already joined this study, we are asking you to continue your participation until July 31 st , 2018 so we can continue to learn more about what factors cause CKD to get worse in children.”	RECOMMENDED CHANGE RATIONALE: The purpose of the study is described under the (heading #2) “Why is this research being done” & study duration is described under (heading #5) “What will happen in this study”
Page 2	<i>3. “Who is doing this study?”</i> <i>4. “How many people will be in this study?”</i>	RECOMMENDED CHANGE RATIONALE: To simplify the two categories of <i>who</i> is doing the study and <i>how many</i> have joined/will be in the study.
Page 2	<i>“Dr. Insert PI’s name is in charge of the study. Insert Coordinator’s name will coordinate the study. Other health care professionals may help them.”</i>	RECOMMENDED CHANGE RATIONALE: To inform participants who will be working on the study at their site.
Page 2	(Deleted “3”) <i>“5.” What will happen if you join this study?</i>	RECOMMENDED CHANGE RATIONALE: Follows consecutive order of numbering for each heading.
Page 2	“However, we plan to extend the study until July 31 st , 2023.”	RECOMMENDED CHANGE RATIONALE: To describe the intent of renewing the study grant for another 5 years.

Page # on the 8/1/17 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Change / RATIONALE FOR CHANGE
Page 3	Deleted “Each participant will be in the study for about one to 13 years”	RECOMMENDED CHANGE RATIONALE: Removed repetitive statement. Length of time in study included in first paragraph under heading #5.
Page 3	“If you are unable to attend future study visits we would <i>like to</i> continue follow up with you on a yearly basis.”	OPTIONAL CHANGE RATIONALE: Denotes wording that implies the continued follow up is optional rather than required.
Page 3	Changed the following: <ul style="list-style-type: none"> “in-person interview or on-line survey” to “in-person interview or <i>an</i> online-survey” 	RECOMMENDED CHANGE RATIONALE: Grammatical changes.
Page 3	<< <i>Only include the next paragraph if your site is participating in the Post RRT Pilot Study</i> >> <i>If your child starts dialysis or receives a kidney transplant we would like to continue seeing you and your child for study visits. These visits are a little different than the visits described in this consent form so we will have you sign a separate consent form to continue in the study.</i>	REQUIRED CHANGE (for sites performing the Post Renal Replacement protocol) RATIONALE: Amendment includes the addition of the post Renal Replacement Protocol pilot study.
Page 3	<i>“For children who are still in diapers, a urine sample may be collected using a urine bag, or by placing cotton balls in the diaper area.”</i>	REQUIRED CHANGE RATIONALE: This applies to any participant that is still in diapers.
Page 3 - 4	Revised the following paragraph: “When the iGFR test is to be completed, your child will come to <i>Insert location of visit</i> in the morning and an IV catheter may be placed. Upon request we can apply EMLA cream or LMX 4 (Elam ax) cream to numb the IV sites. Study blood work may then be drawn from the IV or through separate needle-sticks or finger-sticks, if you prefer....The blood samples can also be obtained through 2 separate needle-sticks or finger-sticks instead of the IV if preferred. If we are unable to obtain the iGFR, you may be asked to reschedule the study visit.” Changed to: <i>“When the iGFR test is to be completed, your child will come to <i>Insert location of visit</i> in the morning. If you would like, we can apply a temporary numbing agent to the skin where needle sticks will occur. An IV catheter may be placed for drawing blood.... The Iohexol test can also be done using 3 separate needle-sticks instead of the IV if preferred. After the Iohexol is given, if drawing blood is difficult, finger sticks may be used to collect the blood samples.”</i>	RECOMMENDED CHANGE RATIONALE: To simplify and clarify that the iohexol GFR test procedure. Also, to allow different types of topical numbing agents to be used based on site resources.

Page # on the 8/1/17 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Change / RATIONALE FOR CHANGE
Page 4	“We will use some psychological surveys and tests to learn about your child’s (deleted “thoughts”) feelings, behaviors, and <i>how they think and learn</i> (cognitive abilities).”	RECOMMENDED CHANGE RATIONALE: Simplified phrasing for easier reading level.
Page 4	Moved statements: “You will <i>also</i> receive (deleted “written”) <i>a</i> feedback report summarizing the results of the psychological testing. (deleted “about your child’s performance on the cognitive tests. Your nephrologist will also receive a copy of this feedback) ...“You will be informed, through your nephrologist, if your answers <i>on the behavioral questionnaires</i> suggest the possibility that your child is at risk for self-injury or injury to others” To “Received test results” (page 6)	RECOMMENDED CHANGE RATIONALE: Information regarding study test results provided should be listed under the heading of ‘Receive test results’
Page 4	<<Only include the next paragraph if your site is participating in the NIH Toolbox Pilot Study>> <i>“Participants who are 3 years old and older will complete some additional thinking exercises using an online program called the NIH Toolbox. The NIH Toolbox is a set of brief tasks used to assess how your child thinks and learns. These online exercises will be completed on an iPad at study visits 1B, 3, 5, and 7.</i> <i>If your child is 8 years old or older they will also answer questions about their feelings. If your child is between 3 to 12 years old we will also ask you to complete questions about your child’s feelings using the NIH Toolbox. These questions will be completed on an iPad starting at visit 1B and every other year after that.”</i>	REQUIRED CHANGE (for sites completing the NIH Toolbox) RATIONALE: Amendment includes the expansion of the NIH Toolbox pilot study to include additional sites.
Page 4	Changed the following: <ul style="list-style-type: none"> • “uses ultrasound” to “uses <i>sound waves</i> (ultrasound)” • “to find abnormalities” to “to <i>look for</i> abnormalities” • “using ultrasound (c-IMT)” to “using ultrasound <i>in a test called Carotid Intima-Media Thickness</i> (C-IMT).” 	RECOMMENDED CHANGE RATIONALE: Grammatical changes that clarify procedure name and mode of action.
Page 5	Changed “radiation (X-rays), sound waves (ultrasound)” to “radiation (X-rays), ultrasound...”	RECOMMENDED CHANGE RATIONALE: Grammatical change as “ultrasound” has already been defined in prior text.
Page 5	<i>“We may ask for you to collect blood pressure measurements on your child at home using a wireless blood pressure machine called the QardioArm. We will give you the machine and teach you how to use it during the study visit. At home you will be asked to collect blood pressure measurements for 3 days.”</i>	REQUIRED CHANGE (for sites performing the Home Blood Pressure) RATIONALE: Amendment includes the addition of the Home Blood Pressure (BP) pilot study.

Page # on the 8/1/17 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Change / RATIONALE FOR CHANGE
Page 5	<i>“If your child is less than 1 year old and/or unable to stand, we will collect the hip and waist measurement at your next visit.”</i>	RECOMMENDED CHANGE RATIONALE: Clarification that waist & hip measurements will only be collected if the participant can stand.
Page 5	<i>“If your child is less than 3 years old we will also measure head circumference at every study visit.”</i>	RECOMMENDED CHANGE RATIONALE: Clarification that head circumference will be collected as part of growth measurements.
Page 5	<i>“If your child is 6 years old or older (deleted “At every other visit beginning at the V3”) we will also measure your child’s hand and forearm muscle strength. To do this, we will use a dynamometer to measure hand grip strength. This will be done starting at the V3 and every other year after that.”</i>	REQUIRED CHANGE RATIONALE: To clarify that the Grip Strength is completed for 6 years old & older.
Page 6	<i>“We may measure your physical activity every year beginning with Visit 1B. To do this, we will ask you to wear a monitor continuously for 8 days. The monitor looks similar to a watch and will be worn on the wrist.”</i>	REQUIRED CHANGE (for sites performing the Physical Activity Monitor) RATIONALE: Amendment includes the expansion of the Physical Activity Pilot Study to include additional sites.
Page 6	<i><<Only include next sentence if the ActiGraph Pilot Study will be done at your site>> In addition, you will also be given a summary of your activity level if you wear the physical activity monitor.</i>	REQUIRED CHANGE (for sites performing the Physical Activity Monitor) RATIONALE: Informing participants that feedback will be provided for the activity monitor.
Page 7	<i>“Before your child’s sample is sent to the Repository, the sample will be given a code number that will not include your child’s name (deleted “and all”) or other personal identifying information, such as address, social security number, and date of birth. (deleted “will be removed”)”</i>	RECOMMENDED CHANGE RATIONALE: Clarification that the repository samples ONLY have a coded number and the sample itself DOES NOT include any personal identifiers that would need to be removed from the sample.

Page # on the 8/1/17 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Change / RATIONALE FOR CHANGE
Page 8 & 13	Capitalized “Honest Broker” throughout document	RECOMMENDED CHANGE RATIONALE: Grammatical change.
Page 9	<i>“Because we want to look at your kidney health over a long period of time, we will continue to check for information even if you were no longer taking part in the study.”</i>	REQUIRED CHANGE RATIONALE: To clarify that if the participant is no longer completing active study visits or the continued follow up, etc. linking data with National Databases will still occur. The participant will need to notify the study team if they no longer wish for information to be collected.
Page 9	“If at a later date you decide you no longer want to participate <i>you must inform the study doctor or study team that you would like to cancel your permission to use your personal identifiers to request your health information from public health databases.</i> ”	REQUIRED CHANGE RATIONALE: To clarify the process for cancellation of participation in data link.
Page 10	(Deleted “4”) 6. What are the risks or discomforts of the study?	RECOMMENDED CHANGE RATIONALE: Follows consecutive order of numbering for each heading.
Page 10	<u>“Urine Collection Bag</u> <i>If your child is still in diapers a urine bag may be used to collect a urine sample. Skin redness or irritation may result from the collection bag but it is rare.”</i>	REQUIRED CHANGE RATIONALE: The use of urine collection bags for the younger cohort may include this added risk.
Page 10	Changed “If the iohexol infiltrates (leaks)...” to “If the iohexol infiltrates...”	RECOMMENDED CHANGE RATIONALE: Grammatical change as “infiltrates” has already been defined in prior text.
Page 10	<u>ABPM or home blood pressure monitor</u> Possible risks associated with use of the ABPM <i>or home blood pressure monitor</i> include discomfort, bruising, or injury to the arm when the blood pressure cuff is inflated.	REQUIRED CHANGE (for sites completing the home BP pilot study) RATIONALE: New study procedure and associated risk to be performed by a subset of sites.

Page # on the 8/1/17 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Change / RATIONALE FOR CHANGE
Page 11	There are no known (deleted “significant risks”) <i>side effects</i> with a cardiac MRI. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. <i>Because MRI uses powerful magnets, the presence of metal in your body may be a safety hazard.</i>	REQUIRED CHANGE RATIONALE: Clarification of why there are steps to be followed including a questionnaire to ensure the safety of this procedure.
Page 11	Neurocognitive Tests <i>or NIH Toolbox assessment</i>	REQUIRED CHANGE (for sites completing the NIH Toolbox) RATIONALE: New study procedure and associated risk to be performed by a subset of sites.
Page 11	<i>“Physical Activity Monitor</i> <i>There are no confirmed side effects from using the ActiGraph monitor to measure activity.”</i>	REQUIRED CHANGE (for sites performing the Physical Activity Monitor) RATIONALE: New study procedure and associated risk to be performed by a subset of sites.
Page 11	(Deleted “5”) 7. Are there risks related to pregnancy?	RECOMMENDED CHANGE RATIONALE: Follows consecutive order of numbering for each heading.
Page 11	Changed “your child would” to “your child <i>will</i> ”	RECOMMENDED CHANGE RATIONALE: Grammatical change

Page # on the 8/1/17 version of the CKiD Consent Form Template	Changes to CKiD Consent Form	REQUIRED, RECOMMENDED, or OPTIONAL Change / RATIONALE FOR CHANGE
Page 11 - 16	<p>(Deleted “6”) 8. Are there benefits to being in the study?</p> <p>(Deleted “7”) 9. What are your options if you do not want to be in the study?</p> <p>Deleted “8”) 10. Will it cost you anything to be in this study?</p> <p>(Deleted “9”) 11. Will you be paid if you join this study?</p> <p>(Deleted “10”) 12. Can you leave the study early?</p> <p>(Deleted “11”) 13. Why might we take you out of the study early?</p> <p>(Deleted “12”) 14. How will your privacy be protected?</p> <p>(Deleted “13”) 15. What if there is a Certificate of Confidentiality for this study?</p> <p>(Deleted “14”) 16. What other things should you know about this research study?</p> <p>(Deleted “15”) 17. Assent Statement</p> <p>(Deleted “16”) 18. What does your signature on this consent form mean</p>	<p>RECOMMENDED CHANGE</p> <p>RATIONALE: Follows consecutive order of numbering for each heading.</p>
Page 16	Updated the CKiD Study Timetable.	<p>REQUIRED CHANGE (for sites performing one or more of the individual pilot studies)</p> <p>RATIONALE: Reflects addition of pilot studies per August 2017 amendment.</p>

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

**SECTION 27: BLOOD PRESSURE MEASUREMENT
TRAINING AND CERTIFICATION**

27.1 OVERVIEW

Before the actual initiation of standardized measurements, training and certification must be provided so that all staff responsible for recording blood pressure readings will be certified as having met a stipulated level of performance. Recertification will be required at yearly intervals for the duration of an observer's service in the CKiD Study.

The certification process includes training and the successful completion of:

- Review Training Blood Pressure (BP) DVD (every year)
- A live evaluation (every year)

The training strategy is a two-stage program.

Each site must have at least one staff member who is certified in blood pressure measurement.

The first stage of the program is the successful completion of the BP DVD test provided by the DCC. The data coordinating center (DCC) has made the BP DVD video files available on the CKiD website at https://statepi.jhsph.edu/ckid/BP_certification.html. Upon request, the DCC can also send the BP DVD to each clinical site. The Blood Pressure Observer(s) must successfully complete this BP DVD test online at the time of certification and every year. An observer will be considered certified if they obtain a score of 85% on the DVD test.

In this second stage, each Blood Pressure Observer will be asked to perform a live evaluation. The Blood Pressure Observer is then responsible for completing the “Live Blood Pressure Evaluation” checklist (see Section 16.2 for the BP Measurement Step-by-Step and Section 28.5 for the Live Blood Pressure Evaluation Checklist). The clinical site will fax the “Live Blood Pressure Evaluation” checklist to the DCC.

The DCC is responsible for identifying who is certified. The Data Coordinating Center will, in addition, remain responsible for overall monitoring and quality control (as will be described in Section 28).

27.2 TRAINING MATERIALS

27.2.1 Overview of Training Materials

Trainees are first oriented to the subject of blood pressure measurement with a series of lectures. A brief description of each is given here.

1. Blood Pressure Measurement - Problems and Solutions (lecture)

A general discussion of blood pressure, the history of its measurement, and some of the problems and solutions inherent in its measurement. (Lecture #1)

2. The Mabis Medic-Kit Aneroid Device (lecture)

An explanation of the mechanics and the principles of the operation of this device and the importance of regular calibration checks. (Lecture #2)

3. Blood Pressure Recording Procedures (lecture)

Step-by-step instructions on how to measure blood pressure using the Mabis Medic-Kit Aneroid Sphygmomanometer. (Lecture #3 and Sections 27.2.4 – 27.3.10)

4. Local Blood Pressure Equipment Maintenance and Mercury Toxicity Safety Responsibility (notes).

For those using mercury manometers for calibration checks.

Step-by-step instructions on how to perform routine maintenance duties on both the Mabis Medic-Kit Aneroid and conventional mercury sphygmomanometers (used for calibration checks every year) (Section 27.2.11).

27.2.2 General Plan

The observer must review the BP DVD or DVD video files on the CKiD website, and successfully pass, with a score of 85% on the BP DVD test every year. The test involves watching aneroid sphygmomanometer and listening to the simultaneous Korotkoff sounds during blood pressure measurements, then recording the systolic and diastolic levels for each on the BP DVD test sheet.

The BP DVD test answers should be submitted online via the test link on the CKiD website: <http://statepiaps6.jhsph.edu/bpc/index.html>. Finally, the observer must demonstrate one or more complete and correct blood pressure determination procedures for 1) cuff selection by correct arm measurement, 2) determination of pulse, 3) determination of peak inflation level using the Mabis Medic-Kit Aneroid, and 4) correct blood pressure measurement following the protocol. The Live Evaluation checklist should be scanned and emailed to the DCC at ckidship@jhu.edu.

27.2.3 Lecture presentations.

27.2.3.1 Lecture #1

Blood Pressure Measurement - Problems and Solutions

Important problems in blood pressure measurement exist, random variation within each subject, and systematic variation sub-classified as follows: "(i) alarmingly large differences in estimation between observers, sometimes as large as 15 mm Hg..., (ii) effects of the circumstances of measurement, both emotional and physical (especially recent physical activity or change of position), (iii) seasonal changes, and (iv) relatively small errors due to overestimation of pressures in fat arms...."

What can be done to deal with these problems: With respect to random individual variation for each person, we obtain multiple readings on each occasion of observation and use as our estimate of blood pressure an average of two readings, always excluding the first inflation of the cuff (used only to estimate the peak inflation level).

What about the systematic biases. As to differences between observers, these are considered as of two types, one type affecting chiefly the mean of a series of measurements, the other type chiefly distorting the reported frequency distribution of readings. This latter type includes terminal digit preference, which is the unconscious tendency to choose one digit over others in assigning the value of a reading and the prejudice against certain values. Factors affecting mean differences between observers include mental concentration or reaction time, hearing acuity, confusion of auditory or visual cues, interpretation of sounds, rates of inflation and deflation of the cuff, and reading of the moving column of mercury.

These problems can largely be overcome by training followed by satisfactory performance on the BP DVD test. The method of training and its specific objectives are therefore worth brief discussion now.

Training in blood pressure measurement will take two forms. First, there will be a viewing of the training BP DVD with demonstration to acquaint you with the proper procedures for measuring blood pressure and also to familiarize you with the Mabis Medic-Kit Aneroid device. Second, you will take actual live blood pressure readings and complete the Live BP Evaluation Checklist. Your ability to measure blood pressure accurately as a result of this training will be tested using a DVD to simulate the fall of mercury with accompanying Korotkoff sounds during an actual blood pressure measurement. You will be required to determine the systolic and diastolic levels for each subject in the film, within predetermined limits.

27.2.3.2 Lecture #2

Mabis Medic-Kit Aneroid Device

Aneroid sphygmomanometers have achieved widespread acceptance in recent years, chiefly as an alternative to mercury devices and their associated disadvantages. An inherent drawback to aneroid devices is the fact they must be checked for calibration at regular intervals (every year in CKiD) and adjusted if necessary. Mercury manometers are still considered the gold standard in blood pressure measurement. **Annual calibration checks for the Mabis Medic-Kit Aneroid must be done.** If clinical sites are unable to use mercury sphygmomanometers for calibration checks at their site, you can send your Mabis Medic-Kit Aneroid Device to the data coordinating center for calibration as

described in Section 27.2.11. Sites must complete the Calibration Check form each time the device is calibrated. If the site sends the aneroid device to the DCC for calibration, the Calibration Check Form should be sent with the device. The DCC will calibrate the device and indicate on the Calibration Check Form that the device was calibrated. When the clinical site receives the calibrated device and completed Calibration Check Form, they must fax the form to the DCC for data entry.

27.2.3.3 Lecture #3

Blood Pressure Recording Procedures

These procedures for blood pressure recording were developed after extensive consideration and discussion of numerous approaches to measurement techniques. In addition to the selection of instruments and specification of criteria for measurement, we specify methods for the entire sequence of steps in blood pressure recording. For all observers, whether inexperienced in blood pressure measurement or accustomed to different procedures, it will be important to become intimately familiar with these procedures and to carry them out, as early as possible, as a matter of habit. As an introduction, the following series of slides is presented to demonstrate the steps involved for the recording of blood pressure. The sequence presented here illustrates use of both the Mabis Medic-Kit Aneroid.

27.2.4 Equipment and Supplies

1. The equipment needed by each observer includes a Mabis Medic-Kit Aneroid sphygmomanometer in good condition,
2. Access is needed to the full set of Mabis Medic-Kit cuff sizes. These are commonly referred to as the infant, child, adult, large adult and thigh cuffs, respectively.
3. The inflation bulb should operate smoothly and should perhaps be individualized to each observer.
4. The stethoscope, in good condition, should be switched for use of the bell in listening to the Korotkoff sounds.
5. A stop watch (provided in the CKiD Starter package), is needed for measurement of the pulse.
6. A Graham-Field disposable measuring tape (provided in the CKiD Starter Package) in metric units is required for determination of the correct cuff size for each participant.
7. A ballpoint pen should be used for all data recording, preferably with medium or larger point, and black ink.
8. Requirements for furniture are simple but must provide for a comfortable resting position of the arm with mid-cuff at heart level and feet resting, not dangling (i.e., place feet on phonebook, stool, storage bin).
9. The Physical Examination (PE) form must be in place before measurement begins.

27.2.5 Arm Measurement

10. Measurement of the arm is required for selection of the proper cuff. For this measurement, the arm should be bare.
11. The measurements are taken on the right arm, with the participant standing, holding the forearm horizontal. Arm length is measured from the acromion or bony extremity of the shoulder girdle, to the olecranon, or tip of the elbow. The full arm length from acromion to olecranon is measured, and the midpoint is marked on the dorsal surface of the arm. With the participant's arm relaxed at the side, the arm circumference is measured by drawing the tape snugly (without indenting the skin) around the arm at the level of the midpoint marking. Care must be taken to keep the tape horizontal.
12. On the PE Form, the chart of arm circumference measurements and corresponding cuff sizes is consulted, and
13. the proper cuff size is checked. Indicate this cuff size on the form. (Note: If an arm measures 33.0, 33.0 will be entered for question E1 (Midpoint circumference of arm being used) on the PE Form. (**Try to use the same size cuff for every measure for a participant.**))

27.2.6 Preparation for Actual Readings

14. The participant should then be seated with the elbow and forearm resting comfortably on a table with the palm of the hand turned upward. The area to which the cuff is to be applied must be bare.
15. The brachial artery is located by palpation and marked, as is the midpoint of the rubber bladder within the cuff. Often this point is marked on the cuff itself; however, it may not be accurate. Therefore, you should identify the midpoint by folding the bladder.
16. The cuff is then wrapped about the arm so that the midpoint of the bladder lies over the brachial artery, and the mid-height of the cuff is at heart level.
17. The Mabis Medic-Kit Aneroid sphygmomanometer is then connected with the cuff.
18. The manometer is positioned so that the observer's can read the dial without a glare.
19. The radial pulse is located.
20. While palpating the radial pulse, observe the dial of the aneroid sphygmomanometer and quickly inflate to 60 mmHg and then slowly inflate in increments of 10 mmHg until the pulse is no longer felt. If the pulse is still detected, the cuff is inflated slowly by increments of 10 mmHg until the pulse disappears. Either the first or the second of these procedures identifies the Observed Pulse Obliteration Pressure.
21. The cuff is quickly and completely deflated.
22. The observed value and 30 mmHg are used to calculate (by addition) the Corrected Pulse Obliteration Pressure. Both are recorded on the PE form.
23. The sum of the two equals the Peak Inflation Level (PIL)

27.2.7 First Blood Pressure Reading

24. To perform the measurement of blood pressure itself, the brachial artery is again palpated and marked with a pen. Note that the arm remains bare.
25. The stethoscope earpieces are put in place with the earpieces positioned forward, and
26. the bell of the stethoscope is placed carefully and without excessive pressure over the brachial artery, just between the elbow crease and lower edge of the cuff.

27. The cuff is quickly inflated to the Peak Inflation Level.
28. The cuff is then deflated very steadily at 2 mmHg per second, to a level 10 mmHg lower than the level of the last Korotkoff sound heard.
29. The manometer level is now dropped quickly to the zero level for this reading.
30. The cuff is then disconnected and the stethoscope removed.
31. The observed values for the SBP, DBP, are recorded on the PE form.

27.2.8 Between Readings

32. If the cuff is uncomfortable for the participant you may remove it.
33. The observer will raise the participant's arm overhead for 15 seconds without the participant's assistance.
34. The arm is then lowered gently for an additional 15 seconds. There is a total of 30 seconds between readings.
35. If the cuff was removed it should be replaced, and the Mabis Medic-Kit Aneroid sphygmomanometer is reconnected.

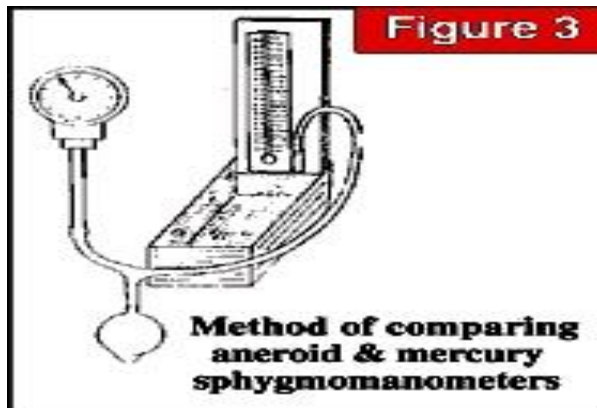
27.2.9 Second Blood Pressure Reading

36. The second reading is carried out exactly as the first.
37. The observed SBP, DBP, are recorded,

27.2.10 Between Readings/Third Blood Pressure Readings

- The cuff may be removed once again and the entire sequence is repeated from having the observer raise the participant's arm overhead for 15 seconds, lowering the arm and waiting an additional 15 seconds before taking the third Blood Pressure Reading. Note: There is a total of 30 seconds between blood pressure readings.
- As before, the observed SBP, DBP, are recorded on the PE form.
- The second and third readings are averaged to get the average systolic and diastolic for the visit.

27.2.11 Calibration of the Mabis Medic-Kit Aneroid



Calibration checks are done annually. You will need the following equipment:

- Mercury sphygmomanometer
- “Y” connector
- Inflation bulb and valve attached

To calibrate the aneroid device do the following and record calibration checkpoints on the Blood Pressure Aneroid Calibration Check Form:

1. Connect one tube to the mercury manometer.
2. Connect the Mabis Medic’s aneroid dial to the other tube. (Cuffs and bags are not used when conducting calibration checks.)
3. Slowly inflate the instruments to 250 mmHg and compare the readings.
4. They should be the same; however a deviation of +/- 4mmhg is acceptable.
5. Record the readings you obtain.
6. Repeat the procedure at 160 mmHg.
7. Repeat at 70 mmHg.

If, when averaged, there is a deviation of greater than +/-4mmHg at any level, the aneroid device being tested is inaccurate and should be mailed to the DCC. Email Jeanne Charleston @ jeannec@jhmi.edu and cc KIDMAC @ ckidship@jhu.edu prior to shipping the device. If necessary, the DCC will send the device back to the manufacture for repair.

Note: Remember, the mere fact that the needle points to zero on the dial of the aneroid manometer when the compression is deflated does not necessarily mean that the instrument is accurate over the entire pressure range. “Primer Of Clinical Blood Pressure Measurement,” by George E. Burch, M.D. and Nicholas D. Pasquals, M.D.

“The readings on the dial at different pressures should check with those of a properly constructed and functioning mercury manometer. The fact that the pointer indicates zero may be no guarantee of accuracy over the whole pressure range”. American Heart Association, “Recommendations for Human Blood Pressure Determinations by Sphygmomanometers”.

If CKiD clinical sites cannot perform annual calibration checks, the site should send their equipment to the following site:

Jeanne Charleston
C/O Johns Hopkins ProHealth
1849 Gwynn Oak Ave, Suite 1
Baltimore, MD 21207
Telephone: 410-281-1138
Email: jeannec@jhmi.edu

Clinical sites must contact Jeanne Charleston, prior to shipping the aneroid device for calibration.

27.2.12 Inspection of the Mabis Medic-Kit Aneroid Manometer

Unless obviously damaged due to dropping or other accident, the Mabis Medic-Kit Aneroid sphygmomanometer is expected to operate without disturbance of its measurement performance. Annual calibration checking must be done to ensure against undetectable accuracy problems.

27.2.13 Documentation of Certification

- A. Each person in the clinical site that will be filling out any part of a blood pressure form will need to be certified. This includes all blood pressure observers.
- C. The Live Blood Pressure Evaluation Checklist should be carefully followed to ascertain that the trainee has a clear understanding of the procedures. This evaluation should be completed by the supervisor as a passive observer. Avoid prompting the trainee. The trainee should complete one or more complete and uninterrupted exercises of the full procedure. Errors of procedure should be reviewed, discussed and corrected during BP certification. When carried out without procedural errors, this record should be completed, signed and faxed to the DCC.
- D. Do not overexpose the trainee to the actual BP DVD test. The test should be submitted online via the test link listed on the CKiD website. If a systematic problem is discovered, the DCC will instruct you as to the type of problem discovered. The specific problem should not be identified to the trainee, as this may artificially bias the trainee's responses. If the problem is not corrected within three DVD tests, the DCC will contact the site to discuss the problems identified and provide instructions over the phone. The Data Coordinating Center will need to have complete documentation of the certification before the trainee can be employed as a blood pressure observer. We suggest keeping the originals in the CKiD Blood Pressure Manual Binder and fax to the Data Coordinating Center. The Data Coordinating Center will instruct the Clinical Coordinating Center who will inform the site when re-certifications should be scheduled, every year.

27.3 CERTIFICATION PROCEDURES AND CRITERIA

27.3.1 Two Steps Needed For Certification

In order to standardize the previously described methods of blood pressure measurement and to ensure that a high level of performance is attained, a two-part training session has been developed. After successful completion, an observer is certified to take blood pressures in the study program. The two steps needed for certification are enumerated below.

1. The first step is a series of blood pressure readings presented on a BP DVD or online video file to test the observer's identification of the systolic and diastolic Korotkoff sounds. This video mimics the actual blood pressure measurement setting by providing a series of blood pressure readings which consist of both aneroid and mercury sphygmomanometers and the audible Korotkoff sounds. An observer is certified if the criteria of the scoring procedure are successfully met. The criteria for the scoring procedure are not available to the Clinical Center or to the observers. The scoring will be done at the DCC.
2. The second is the successful completion of The Live Blood Pressure Evaluation. Each observer is to verify the correct procedure for blood pressure measurement by observing the observer in one or more complete and uninterrupted exercises of the full procedure. When carried out without procedural errors, this record should be completed, signed and faxed to the DCC. Errors of procedure should be reviewed, discussed and corrected, until one completed determination is accomplished without error.

As a means of maintaining a high level of quality and standardization over time, blood pressure observers will be recertified in the BP DVD test and live evaluation every year. Re-certification will involve repeated testing by viewing the BP DVD test video and submitting test answers online, as well as live measurement evaluation. The Data Coordinating Center will notify the clinical sites as to the schedule and requirements of the recertification. A further description is in Section 27.3.2.

27.3.2 Instructions for Taking the DVD Test

Viewing of the BP DVD test may be done in a group or individually. The DVD test can be viewed as a video file online or via the DVD included in the site's BP training manual. The DVD test consists of twelve systolic and diastolic sequences. After each sequence, the observer should record, on the recording sheet provided online, the systolic and diastolic reading for that sequence. All entries should then be submitted online via the test link: <http://statepiaps6.jhsph.edu/bpc/index.html>. Leading 0's should be entered if appropriate. The manometer in the BP DVD test video is read exactly as one would be read in actual practice. Each blood pressure should be read to the nearest even digit. The DVD test video also includes a blood pressure with an auscultatory gap.

27.3.3 The Study Forms Required For Certification Procedures

The two study forms required for certification every year include:

1. The BP DVD Test (online); and
2. The Live Blood Pressure Evaluation Checklist.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY
SECTION 28: BLOOD PRESSURE MEASUREMENT
QUALITY CONTROL

28.1 Overview

There are two primary methods for monitoring the performance of trained observers in the measurement of blood pressures during the course of an observational study. The first is the completion of an Annual Recertification set of procedures. The second is the twice per year monitoring by the Data Coordinating Center of all observers for digit preference.

In addition to these, CKiD has adopted and instituted a comprehensive program to insure the collection of high quality blood pressure measurements. Factors contributing to this include:

1. Recruitment of the most qualified personnel.
2. Standardized training and certification every year.
3. Retraining of observers having difficulties with standardized measurements.
4. Annual observations, using the "Live Blood Pressure Evaluation" checklist at the end of this section. One checklist is used for each blood pressure observer. The original should be kept on file and will be reviewed at site visits.
5. Continuous editing and analysis of data by the Data Coordinating Center.
6. Presentation of data analyses to the Clinical Coordinating Centers by the Data Coordinating Center to provide feedback twice per year (i.e., digit preface).
7. Annual Calibration.
8. Documentation of the "Live Blood Pressure Evaluation" Checklist will be sent to the DCC. The dates of the Mabis Medic-Kit Aneroid Sphygmomanometer annual calibration checks will be entered on a data collection form.

28.2 Annual Recertification and Retraining

As with the initial certification process this recertification process (every year) includes the successful completion of:

- * a BP DVD test sheet
- * a Live Evaluation Checklist

It is recommended that person performing blood pressure measurements demonstrate the live evaluation centrally each year.

The recertification procedures will be conducted at the clinical sites. However, scoring of the DVD tests will be done by the DCC. The Live Evaluation Checklist and DVD test should be faxed to the DCC. The confirmation from the DCC showing all staff members measuring blood pressures have successfully completed the DVD test should also be faxed to the clinical centers. The DCC is responsible for identifying who is a certified blood pressure observer. A report based upon the results of these tests may be presented to the Steering Committee. This report would describe how well the observers are measuring blood pressure levels under standardized conditions, and how many observers had difficulty being recertified.

Of course, the results of the tests may indicate that an observer may need to be retrained in some or all aspects of blood pressure measurement. If this is required, this person will discontinue the measurement of blood pressure levels for the trial until he or she is successfully recertified by the Data Coordinating Center. Central retraining may be required.

Also, if an observer misses a recertification cycle, he or she must repeat the training program.

28.3 Monitoring for Digit Preference

It is well documented in other large blood pressure studies that even well trained observers have the capability to lapse into an unconscious digit preference over time. Digit preference is defined as a predilection to record the terminal digit of a blood pressure measurement as either a "0", or a "2", or a "4", or a "6", or a "8", rather than the actual value. For example, an observer with a "0" digit preference may record an 82 mm Hg DPB (or a 78 mm Hg) as 80 mm Hg.

NO OBSERVER SHOULD EVER HAVE A DIGIT PREFERENCE.

The recertification process should dampen, on an annual basis, any incipient digit preference, but twice per year monitoring and presentation of actual blood pressure measurements by the Data Coordinating Center will identify problems more immediately. If a problem is identified, the blood pressure consultant (Jeanne Charleston) to the CKiD (or his designee) will be notified and corrective procedures implemented. Possible re-training and recertification may be necessary before the regularly scheduled certification.

28.4 Responsibilities of the Data Coordinating Center

It is the responsibility of the Data Coordinating Center to provide training and to monitor the certification of members conducting BP measurements. **It is primarily the responsibility of the person receiving training to train at least one other observer.** However, only the Data Coordinating Center is able to certify an observer, as described above.

If, between re-certifications, the Data Coordinating Center has evidence that an observer is not performing well, the DCC will contact the site to discuss the matter. It may be necessary for the Data Coordinating Center to temporarily rescind a certification and retrain the observer. In this case, until the observer is recertified, he or she may not take blood pressure measurements for CKiD.

It is also the responsibility of the Data Coordinating Center to monitor the specific activities of the bp Observers. In addition to the continuous monitoring of all incoming blood pressure data (e.g., for digit preference or bad values), and the files of the "Live Blood Pressure Reading Performance Evaluation" checklists and should be faxed to the DCC and will be reviewed at each site visit for completeness and accuracy. Also at these site visits, the observers themselves will undergo checklist monitoring.

28.5 **LIVE BLOOD PRESSURE EVALUATION CHECKLIST**
(Used for Certification/Recertification and for Quality Control)

The original should be kept on file at the Clinical Site and a copy should be sent to the DCC.

Trainee's Name: _____

Date: ___/___/_____

Site: _____

Site #: ___

A. Equipment and Supplies

The trainee should indicate that all equipment and supplies needed for blood pressure measurements are present. Check each item as identified:

- _____ (1) Mabis Medic-Kit Aneroid Sphygmomanometer
- _____ (2) Mabis Medic-Kit Cuffs - full set of 5 sizes
- _____ (3) Stethoscope with a bell
- _____ (4) Mayo stand or bedside table
- _____ (5) Accusplit (model 80226) Stopwatch (provided in CKiD starter package)
- _____ (6) Measuring tape
- _____ (7) Black ball point pen
- _____ (8) Physical Exam Form (PE Form)

B. Arm Measurements

The following steps are properly carried out:

- _____ (1) Participant standing
- _____ (2) Arm bare from elbow to shoulder
- _____ (3) Arm at 90 degree angle
- _____ (4) Arm length measured from the acromion (or bony extremity of the shoulder girdle) to the olecranon (or tip of the elbow)
- _____ (5) Midpoint of arm marked at dorsal aspect
- _____ (6) Arm relaxed at side
- _____ (7) Circumference measured with tape horizontal
- _____ (8) No indentation of skin
- _____ (9) Mark at midpoint of arm
- _____ (10) Value checked with chart to ascertain proper cuff size
- _____ (11) Proper cuff size checked on study form (PE Form)

C. Preparation for BP Readings

- _____ (1) Brachial artery palpated
- _____ (2) Midpoint of bladder within the cuff located
- _____ (3) Cuff applied with midpoint of bladder over brachial artery
- _____ (4) Arm positioned with midpoint of cuff width at "heart" level; lower edge 2 to 3 cm (1 inch) above crease
- _____ (5) Wait 5 minutes
- _____ (6) Mabis Medic-Kit Aneroid sphygmomanometer connected to cuff
- _____ (7) sphygmomanometer scale (midpoint) is at eye level
- _____ (8) radial pulse located
- _____ (9) cuff is inflated quickly to 60 mm Hg
- _____ (10) cuff is further inflated slowly by increments of 10 mm Hg (if pulse present at 60 mm Hg) until the pulse is no longer felt.
- _____ (11) cuff is quickly and completely deflated
- _____ (12) Observed Pulse Obliteration value is correctly recorded on the form
- _____ (13) the Correct Pulse Obliteration Pressure + 30 are added to get the Peak Inflation Level

D. Measurement of Blood Pressure

- _____ (1) Brachial artery palpated
- _____ (2) Stethoscope in ears
- _____ (3) Bell over artery, without cuff or tubing contact
- _____ (4) Cuff inflated quickly and smoothly to the Peak Inflation Level
- _____ (5) Deflation at 2 mm Hg/second to 10 mm Hg below K5
- _____ (6) Cuff quickly and completely deflated
- _____ (7) Cuff disconnected
- _____ (8) Recording of SBP and DBP values

E. Between Readings

- _____ (1) Cuff removed or tubing disconnected if uncomfortable
- _____ (2) Arm raised passively overhead for 15 seconds. (Make sure the patient is not supporting the arm at all)
- _____ (3) Arm lowered and cuff replaced with attention to brachial artery and midpoint of bladder; lower edge 2 to 3 cm (1 inch) above crease of the elbow. Note: There is a total of 30 seconds between readings.
- _____ (4) Cuff reconnected

- F. Second Seated Blood Pressure Reading
_____ (1) Conforms with procedures as in E and F above
- G. Third Seated Blood Pressure Reading
_____ (1) Conforms with procedures as in E above
- H. Completion
_____ (1) Complete PE Form
_____ (2) Closure of Mabis Medic-Kit Aneroid manometer case for storage

I certify that all steps were followed correctly and according to the CKID Cohort Protocol.

BP Observer Signature

Remarks: _____

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 29: FITNESS MEASUREMENTS (6 MINUTE WALK & GRIP STRENGTH TESTS)

29.1 THE 6 MINUTE WALK TEST

As of the June 2016 Protocol Amendment, the study discontinued collecting 6 Minute Walk Test (6MWT) data. When the test was performed, this section provided a detail description regarding how to administer the 6 Minute Walk Test (6MWT) and provides documentation on how it was administered and data was collected in the study.

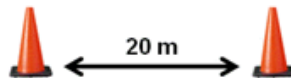
The purpose of the 6MWT is to find out how far the patient can walk in 6 minutes. This test should be performed at Visit 3 and every other year thereafter.

- Prior to administering the test, sites should ensure that the following criteria are met:
 - The participant is six (6) years of age or older at the time of the test
 - The participant has the ability to walk unaided (no crutches, cane, leg braces, wheelchair)

29.1.1 COURSE SETUP

The 6MWT must be performed in a hallway or outdoors. The following guidelines to set up a course for the test:

- A hallway with a clear path of at least 20 meters (one way) or 40 meters per lap. Position a strip of tape at each end of the track so that you can see the beginning and end of the track. If the CKiD cone is not available, use a narrow object (i.e., a small block) that does not force the child to walk further. Position the objects at the edge of the track but within the track length (not on the tape or past the tape).
- If the test is performed outdoors, the path should be straight—no corners or curves. The path must be on a flat surface (e.g., a paved area). The path should be set up outdoors. The path must be on a flat surface (e.g., a paved area). The path should be set up outdoors. The path must be on a flat surface (e.g., a paved area).



- It may be helpful to have a second person help administer the test. Have a person at each end of the track to remind the child to go around the object at that end.

Secure materials needed:

- CKiD cones
- Masking tape
- Measuring tape
- Stopwatch
- Tally counter (if available)
- Wet-erase marker (if tape is unavailable)

29.1.2 PRE-TEST MEASUREMENT: RIGHT-LEG LENGTH

Before beginning the test you must measure the child's right leg length. Record this measurement on the PE form. Ask the child to lie supine on their back with both legs extended and in neutral rotation. In centimeters, measure the distance from the apex of the right anterior iliac spine (ASIS) to the distal right malleolus (see figure 29.1.2 and below).

3 times and the PE

For a on how le

Repeat the measurement record each on form.

demonstration measure right refer to the



www.youtube.com/watch?v=Md-j1SN5Ngw

Length Measurement from ASIS to Medial Malleolus



Figure 29.1.2: Anatomical Location of the ASIS (Anterior Superior Iliac Spine):

29.1.3 PRE-TEST MEASUREMENTS: BLOOD PRESSURE AND PULSE

The standard CKiD measures of blood pressure and pulse should be taken at some point prior to the 6MWT (not afterwards).

29.1.4 TEST INSTRUCTIONS

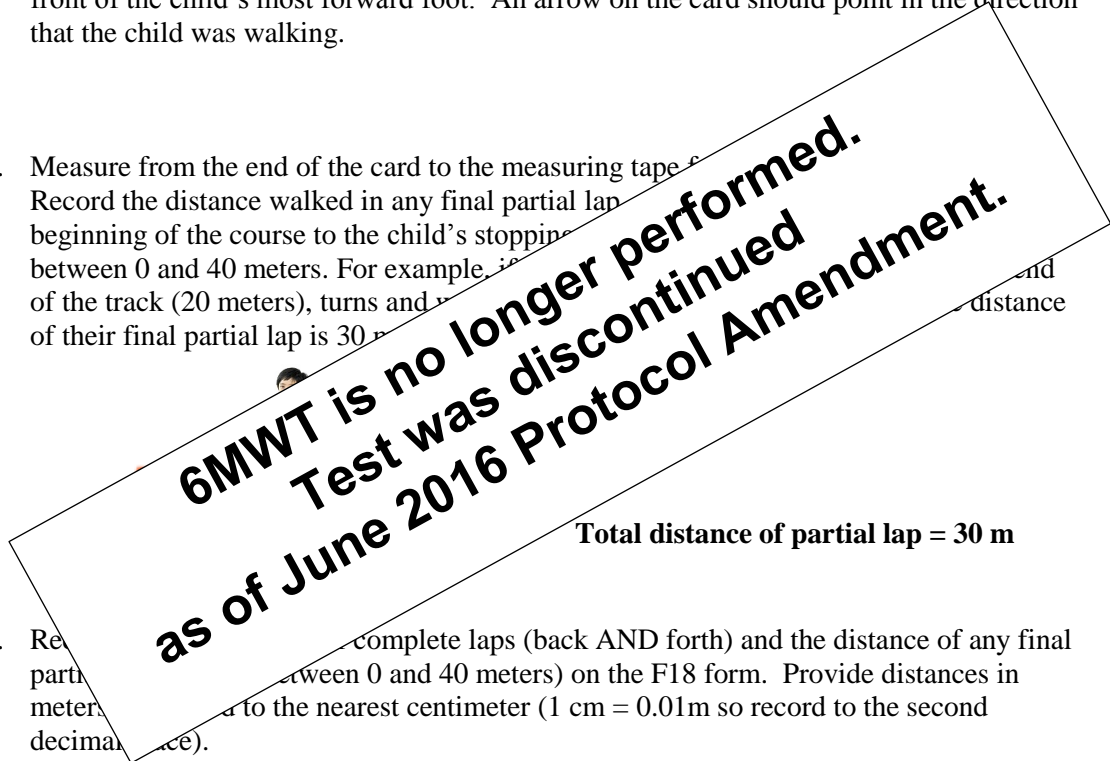
The following instructions describe how to administer the 6 minute walk test.

1. After walking to the test site, have the child rest for 5 minutes. No jumping, walking, or running is allowed. This time is a good time to explain the test to the patient and family.
2. Inform the child/family that the purpose of the test is to find out how far the child can walk in 6 minutes. Before the test, walk with the child along the length of the track to show the beginning and end of the course. Instruct the child ***“Walk to the end of the track, touch the (object), walk back to the other end, and keep going for 6 minutes.”*** Demonstrate how this is done.
 - Note: Instruct the child to walk like they are walking normally. They should walk to go, but hopping, skipping, running, or jumping is not allowed. Remind the child that they can stop to rest during the test.
 - Note: Family members should not encourage or direct the child.
 - Note: Do not allow the child to use headphones or listening to music during the test. This may decrease effort and motivation.
3. Stand at the starting line and behind the starting line and begin walking on the track. Use verbal countdowns like ***“ready, set,”*** or ***“1, 2, 3...”*** as these are used to start the test.
4. Remind the child to go around the object at each end of the track. One complete lap consists of walking from the starting line to the end of the track, turning, and walking back to the starting line. Stand at the starting line throughout the test and make a tick mark on the score sheet to indicate a completed lap each time the child passes the starting line.
 - Note: Do not count out loud and do not rely on memory. Some children start to swing “wide” or walk curvy lines so remind the child to do their best to walk in a straight line.
5. Give standard phrases of encouragement at 30-second intervals. **You may only say *“You are doing well,” “Keep up the good work,”* or *“Keep going.”* Avoid other verbal encouragement (or nonverbal gestures) to speed up.** If the child stops to rest, tell them they can continue whenever they can (clock doesn’t stop).
6. Tell participants how much time remains at each minute by saying simply ***“You have 5 minutes left”*** and so on. At the end of 6 minutes, tell the child ***“Stop and do not move until I come to you.”***

**6MWT is no longer performed.
Test was discontinued
as of June 2016 Protocol Amendment.**

7. Walk to the child and put an index card or a slip of paper on the floor in line with the front of the child's most forward foot. An arrow on the card should point in the direction that the child was walking.

8. Measure from the end of the card to the measuring tape. Record the distance walked in any final partial lap from the beginning of the course to the child's stopping point. If the child stops between 0 and 40 meters. For example, if the child stops 25 meters from the beginning of the track (20 meters), turns and walks 5 meters to the end of their final partial lap is 30 meters. Record the distance



Total distance of partial lap = 30 m

9. Record the number of complete laps (back AND forth) and the distance of any final partial lap (between 0 and 40 meters) on the F18 form. Provide distances in meters and centimeters to the nearest centimeter (1 cm = 0.01m so record to the second decimal place).

- Record the number of meters (0-39) before the decimal point:

___ . ___ (m)

- Record the number of centimeters (0-99) after the decimal point:

___ . ___ (m)

Examples of how to record partial lap measurements:

Partial lap distance measured:	Measurement as recorded on form:
25 meters and 30 centimeters	<u>2</u> <u>5</u> . <u>3</u> <u>0</u> (m)
Exactly 10 meters	<u>1</u> <u>0</u> . <u>0</u> <u>0</u> (m)
50 centimeters	<u>0</u> <u>0</u> . <u>5</u> <u>0</u> (m)
3 meters and 6 centimeters	<u>0</u> <u>3</u> . <u>0</u> <u>6</u> (m)

29.2 THE HAND GRIP STRENGTH TEST

This section describes how to administer the hand grip strength test. The purpose of the hand grip strength test is to measure isometric grip strength using a handgrip dynamometer. This test should be performed at Visit 3 and every other year thereafter.

29.2.1 PRIOR TO ADMINISTERING THE HAND GRIP STRENGTH TEST

Prior to administering the hand grip strength test, the site should ensure that the following has been completed.

1. Confirm eligibility

The test should be completed if the participant:

- is six (6) years old or older at the time of the visit
- has at least one hand without visible limitations (i.e., wearing cast/bandage, missing digits, paralysis)
- has not had surgery performed on either hand within the past three (3) months
- is not using a wheelchair

2. Secure materials needed:

- Hand-grip dynamometer
- AAA batteries
- Wet-erase marker
- Stopwatch
- Sanitizer
- Support pad (if available)

3. Introduce the Hand-Grip Test to participants

- *“In this exam, we want to get some information about your muscle strength. We will be asking you to squeeze as hard as possible with each of your hands. I will explain this in more detail in a few minutes but first I want to ask you a few questions.”*

4. Administer the Pre-Hand-Grip Test Questionnaire.

5. Ask participant to remove hand and wrist jewelry.

6. Demonstrate and have participant complete two warm-up exercises on hand or hands to be tested:

- Shake both hands three (3) times
- Bend and stretch all fingers three (3) times

7. Introduce grip size adjustment:

- *“Next, I am going to adjust this device to fit your hand(s). Please hold this with your (right/left hand).”*

- Place dynamometer on participant's lap and have participant grip dynamometer with the hand that will be tested first. The four fingers should be wrapped around the handle and the thumb should be wrapped around the base of the dynamometer; the participant's hand should be in line with the wrist and forearm (see Figure 29.2.1)
 - i. Note: If the site has a support pad, then the support pad can be placed in the participant's lap and the dynamometer placed on the pad. If no support pad is available, then it should be placed in the participants lap or use a flat, comfortable surface situated at a height that allows the hand to be in line with the wrist and forearm.
 - Adjust the grip size so that the second joint of the index finger is at a 90° angle on the handle (90° flexion between proximal and middle phalangeal point). The grip size can be adjusted by turning the adjustment knob either clockwise or counterclockwise to increase/decrease the distance between the blue and red bars (see Figures 29.2.2-29.2.4).
 - i. If the participant's finger nails are hitting their palm, adjust the dynamometer to a larger grip size.
 - ii. If you are unable to bend the second joint enough to attain a 90° angle for any reason (i.e. arthritis, long nails, large or small hand), adjust grip size to be as close as possible and proceed. Be sure to indicate the reason in the Pre-Hand-Grip Test questionnaire.
 - Move the dynamometer to the other side to test the grip size for the participant's other hand. Most of the time, the grip size will be the same for both hands. If the grip size is different because the participant's hand sizes are different, then the coordinator may choose one of the following options:
 - i. Option 1: Perform the grip strength test on the same hand 6 times with 60 second breaks between each test
 - ii. Option 2: Perform the grip strength on one hand 3 times with 60 second breaks between each test. Then adjust the grip size for the other hand (repeating the grip size procedure in step 6) and perform the grip strength test 3 times with 60 second breaks between each test.
8. Demonstrate grip test for the participant:
- *“For the test, I will ask you to squeeze this hand grip as hard as you can. You will stand with your feet hip width apart and your toes pointing forward like this. You will position your hand so that it's not touching your body and squeeze the handle. I want you to stand tall and try not to lean when you squeeze. You will take a breath in, then blow out while you squeeze. You will squeeze as hard as you can until you can't squeeze any harder. Like this.*

(Do the squeeze demo)

*If testing both hands, say: **We will test each hand 3 times.***

*If testing same hand, say: **We will test your hand 6 times”***

- The guidelines below are for demonstrating the hand -grip test. Make sure the participant understands and follows these guidelines when it is his/her turn. (Refer to Figures 29.2.5 and 29.2.6 for a visual aid).
 - i. Grasp the dynamometer between the fingers and the palm at the base of the thumb.
 - ii. Hold the dynamometer in line with the forearm at thigh level so that it is not touching the body; elbows should not be bent.
 - iii. Emphasize that the participant should stand with their feet hip width apart and toes pointing forward.
 - iv. Instruct the participant not to hold his or her breath. (Take a breath in before starting the squeeze, then blow out the air during the squeeze.)
 - v. Emphasize the quickness and hardness of the squeezing motion (with fist slightly shaking).
9. Have the participant do a practice trial:
- Ideally, the practice trial should be conducted on the hand that will not be tested first. In the event that the same hand must be tested first, a period of 60 seconds should pass between the practice trial and actual trial.
 - Turn the dynamometer on and hand it to the participant. Instruct the participant to grasp the dynamometer between their fingers and the palm at the base of their thumb. Tell them to hold the dynamometer in line with their forearm at thigh level so that it is not touching the body.
 - Make sure the participant has:
 - i. Stance with the feet hip width apart and even, toes pointing forward
 - ii. Knees comfortable but not bent
 - iii. Shoulders back and chest up
 - iv. Head level
 - v. Eyes straight ahead
 - vi. Both arms at side, not touching body, with palms facing inward
 - vii. Elbows comfortable but not bent
 - Remind the participant that neither the hand nor dynamometer should touch the body or any other object during the test.
10. Instruct the participant:
- *“Now try it once just to get the feel of it. For this practice, just squeeze gently. Ready, take a breath in, let it out, squeeze gently.”*

11. Take the dynamometer and press the **“ON/Clear”** button to clear the practice trial.
 - Note: It is important to clear the dynamometer between each trial. If it is not cleared, it will automatically display the average instead of the actual value.
 - Note: If the dynamometer begins to malfunction, change the batteries. If the issue persists, contact your CCC. Examples of problems due to malfunction include:
 - i. Questionable values (e.g., the same reading keeps coming up, the readings have wide variability, or the readings appear inconsistent with the observed effort)
 - ii. The reading on the dynamometer quickly disappears before it can be recorded (this may happen if the dynamometer handle gets jostled).

29.2.2 ADMINISTERING THE HAND GRIP STRENGTH TEST

The following directions describe how to administer the Hand Grip Strength Test. Make sure that all steps in Section 29.2.1 have been completed before beginning the test.

1. Give the dynamometer to the participant’s non-practice hand (i.e. the hand they did not use in the pre-test). Instruct the participant to squeeze as hard as they can, ensuring that they maintain proper form. (Refer to the Pre-Test in Section 29.2.1 for directions on maintaining proper form.)
2. When the participant is done squeezing:
 - Start the stopwatch
 - Take back the dynamometer
 - Record the data in to the Hand-Grip Test Form (F19 Form)
 - Press **“ON/Clear”** to clear the data
 - Note: If the participant does not maintain proper form during a Hand-Grip test, that trial should not be recorded. Remind the participant about the importance of proper form and wait 60 seconds before retesting that hand and moving on.
3. In addition to recording the grip strength, also record the effort exerted for each trial. **‘Maximal effort’** should be recorded only if you notice the participant’s fist slightly shaking when they squeeze; otherwise, record **‘Questionable effort’**.
 - Note: The participant should not excessively shake the dynamometer. Some shaking will occur during a trial with maximal effort; use your judgment as to the appropriateness of shaking.
4. After completing the first grip test, wait 60 seconds before giving the dynamometer to the participant’s other hand to perform the second grip test.
5. Repeat the grip test procedure until each hand has been tested 3 times (or 6 on the same hand if only one hand able to be tested) for a total of 6 grip tests. Wait 60 seconds between each test.
 - Note: Pay special attention that the participant maintains proper form, that you clear the dynamometer after each test, and that the appropriate grip size is being used (if the grip size was different between hands).
6. After completing the Hand-Grip Test, turn off the dynamometer, remove the batteries, sanitize the grips, and put the dynamometer away in its case.

29.2.3 HAND GRIP STRENGTH ILLUSTRATIONS

ADJUSTING GRIP SIZE

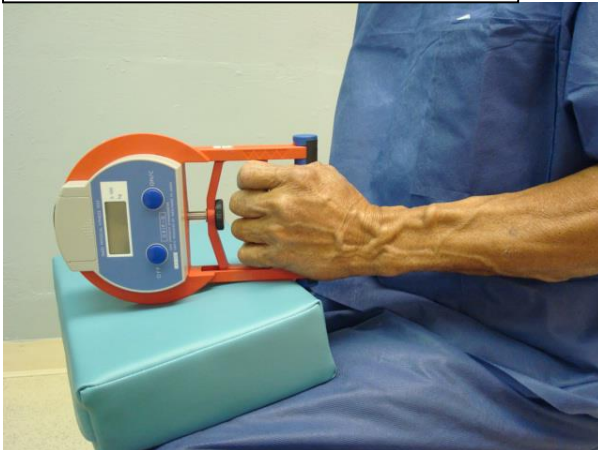


Figure 29.2.1: 90° angle of index finger (front image)

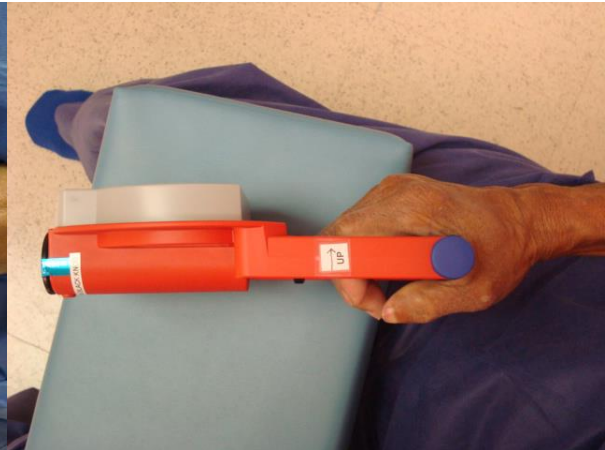


Figure 29.2.2: Checking angle of index finger

Figure 29.2.3: Proper handgrip fit



Figure 29.2.4: Proper adjustment of grip size



Figure 29.2.5: Proper Form during Hand-Grip Test



PROPER TESTING FORM

Head

- ✓ Straight
- ✓ Eyes Facing Forward

Arm

- ✓ Straight Down Side

Wrist

- ✓ Neutral Position
(Not Flexed or Extended)

Feet

- ✓ Hip Width Apart
- ✓ Even



Shoulder

- ✓ Slightly Abducted (~10°)

Torso Posture

- ✓ Upright
- ✓ "Shoulders Back, Chest Up"

Forearm

- ✓ Neutral Position

Figure 29.2.6: Improper Form during Hand-Grip Test



Note: All pictures in Figures 29.2.1 – 29.2.6 above were obtained from the National Health and Nutrition Examination Survey (NHANES) Muscle Strength Procedures Manual, published in April 2011. The manual is available online at: http://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/Muscle_Strength_Proc_Manual.pdf.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

**SECTION 30: GUIDELINES FOR REQUESTING
CKiD REPOSITORY SAMPLES AND/OR PUBLIC DATA**

30.1 OVERVIEW OF PROCESS FOR REQUESTING SAMPLES FROM THE NIDDK REPOSITORY FOR ANCILLARY STUDIES

As defined on the NIDDK website, “An ancillary study is defined as a study that uses the Parent Study (i.e., CKiD) subjects’ data and/or biological specimens, but proposes research questions that are not addressed by the CKiD Study and/or written into its protocols and procedures. In general, ancillary studies are characterized as being outside the specific scientific objectives of the CKiD Study and are funded by a funding mechanism that is separate from the CKiD Study funding mechanisms. Ancillary studies must be approved by the CKiD Study.”

There are three NIDDK central repositories for the CKiD study: NIDDK Biological Repository and Rutgers DNA Repository and NIDDK Data Repository (Information Management Services, IMS). Please note that while the CKiD study is on-going, **investigators interested in receiving repository samples must obtain approval from the CKiD Steering Committee (SC)**; however, **investigators interested in receiving publicly archived CKiD datasets can obtain the CKiD public datasets without SC approval** (refer to Section 30.9 for details). Requesting samples from the NIDDK central repositories for CKiD ancillary studies is a multi-step process. In order to request NIDDK samples for an ancillary study the person requesting the samples must:

1. Be the Principal Investigator (PI) or Data Coordinating Center (DCC, also referred to as KIDMAC) contact of an approved ancillary study.
2. Receive approval from the DCC to enter a sample request.
3. Submit an application for a sample request through NIDDK’s Central Repository Website.

Sections 30.2 – 30.8 in this document outlines the steps in making a sample request from NIDDK biological or DNA repositories for ancillary studies that have been approved by the CKiD SC.

30.2 RECEIVING APPROVAL FROM THE DCC

Prior to requesting samples or data from the NIDDK central repositories, principal investigators must obtain approval from the CKiD Steering Committee. The submission process for obtaining Steering Committee approval is detailed in Section 22 of the Manual of Procedures, CKiD Publication Policy. However, a brief description of the process includes: a) the submission of a concept sheet proposal form, b) the review of the proposal by Steering Committee, Subcommittee members (if appropriate), c) formal critique of proposal and d) CKiD SC decision. The DCC approval letter is provided on behalf of the CKiD Steering Committee. Specifically, once the concept sheet is approved by the CKiD Steering Committee, the PI receives the following:

1. Concept Sheet approval letter
2. Information for the NIDDK website: <https://www.niddkrepository.org>
3. Request Checklist Form

The Request Checklist Form must be completed and emailed to Judith Jerry-Fluker at the DCC at jjerry@jhu.edu.

30.3 OBTAINING THE PAPERWORK REQUIRED TO SUBMIT AN ONLINE APPLICATION

After receiving approval from KIDMAC (i.e., the DCC), the PI must submit an online application on the NIDDK Central Repository website: <https://www.niddkrepository.org>

Please note that you cannot begin the online application upload process until you have completed these steps:

1. Obtain Institutional Review Board (IRB) approval from PI's institution
2. Log in on the NIDDK website (or create a New User Account)
3. Download, complete, and obtain all appropriate signatures for the Sample and Data Use Certificate (SDUC) application

30.3.1 Obtain IRB Approval

The PI must obtain approval for their ancillary study from their Institutional Review Board (IRB) or Human Studies Protection Panel before samples will be released. The IRB approval letter must be uploaded to the sample request application.

30.3.2 Log In or Create a New User Account on the NIDDK Website

In order to access the application, the PI or DCC contact first needs to create a User Account on the website or log in to their existing account.

1. Go to <https://www.niddkrepository.org>
2. Click on "Log in or Register" on the upper right-hand corner of the page.
3. Click "Log in with your IMS Login Service account" link.

Login

[Log in with your NIH Network account](#)

[Log in with your IMS Login Service account](#) 

There are two ways to log into the NIDDK Central Repository website:

1. If you are an NIH employee and have an NIH Network account, click on the NIH link above and log in with your NIH credentials.
2. If you are already a registered user of the NIDDK Central Repository website and don't work at NIH, click on the IMS Login Service link above and follow the instructions.

If you are a new user (outside NIH) [register here](#). If you were a registered non-NIH user prior to September 9th, 2013, then you will need to [register](#) using the same email address as your former account.

Once you are registered, you will use the IMS Login Service link to log in.

*** Note: new accounts require separate email confirmation ***

4. If you have an account, then sign in using your Login Name and Password.
If you do not have an account, then you will need to create a New User account:

- 1) Click on "New user? Create an account"

IMS Login Service

This is a service that allows members to log into participating portals and web applications administered by Information Management Services, Inc.

Username:

Password:

[Forgot your username or password?](#)

[New user? Create an account](#) 

Need assistance? E-mail the [administrator](#) and include details about the system you are trying to access.

Notice: This login service may be used to authorize access to U.S. Government or private computer systems. Unauthorized access or use of this system may subject violators to criminal, civil, and/or administrative action.

- 2) Input all information to request a new account, including reason for requesting an account.

IMS Login Service

Apply For A New Account

Your new account can be used to log into participating portals and web applications that use the IMS Login Service. Please [contact us](#) if you have questions about the process.

All fields are required.

Profile Information

First Name:

Last Name:

Email Address:

If you were invited to create an account by another system, please make sure to use the email address that received the invitation.

Verify Email Address:

Phone Number:

Used for account verification.

Choose a Username

At least 3 characters long.
Letters and numbers only.

Username:

Usernames are case-sensitive.
Recommend using one that's easy to remember such as a combination of your last name and first initial.

Choose a Password

Passwords must be at least 8 characters long and include characters from **at least 3** of the following:

Uppercase letters (A-Z)
Lowercase letters (a-z)
Numerals (0-9)
Special characters (! # \$ % & * + = , - . / : ; () < > ? @ \ ^ _ ` ~)

Passwords will expire every 60 days.

Password:

Confirm Password:

Security Questions

Question One:

Answer One:

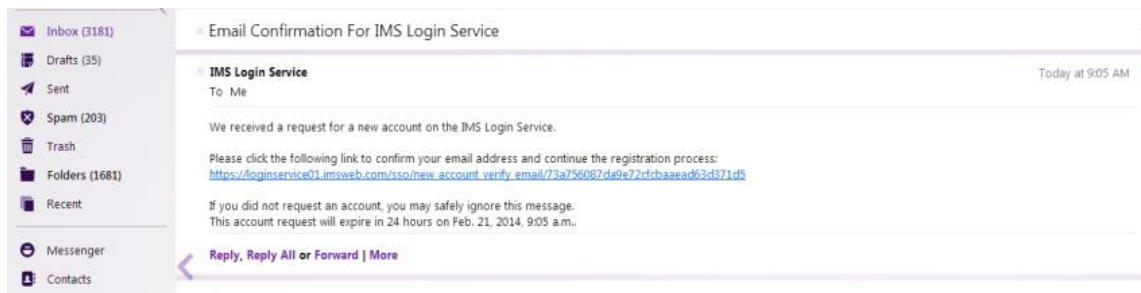
Note: Answer is not case-sensitive

- 3) After you have submitted all the requested information, the following message will appear.

Account Request Received

You will be receiving an email from us shortly. Please verify your email address by following the link located in the email. The account creation process cannot continue until you do so.

- 4) Once the new account request is submitted, you will receive an automated email. You must click on the link in the email to verify the email address you provided.



5) After you click on the link, the following message will appear:

You have successfully verified your email address

Thank you for verifying the email address for user **ubicd**. Your account will now continue through the approval process. Please expect to hear from us soon regarding your account.

6) At this point, you have completed your portion of the new account request process. However, the account will still need to be approved by NIDDK CR personnel. Once the account is approved, you will receive an approval email.

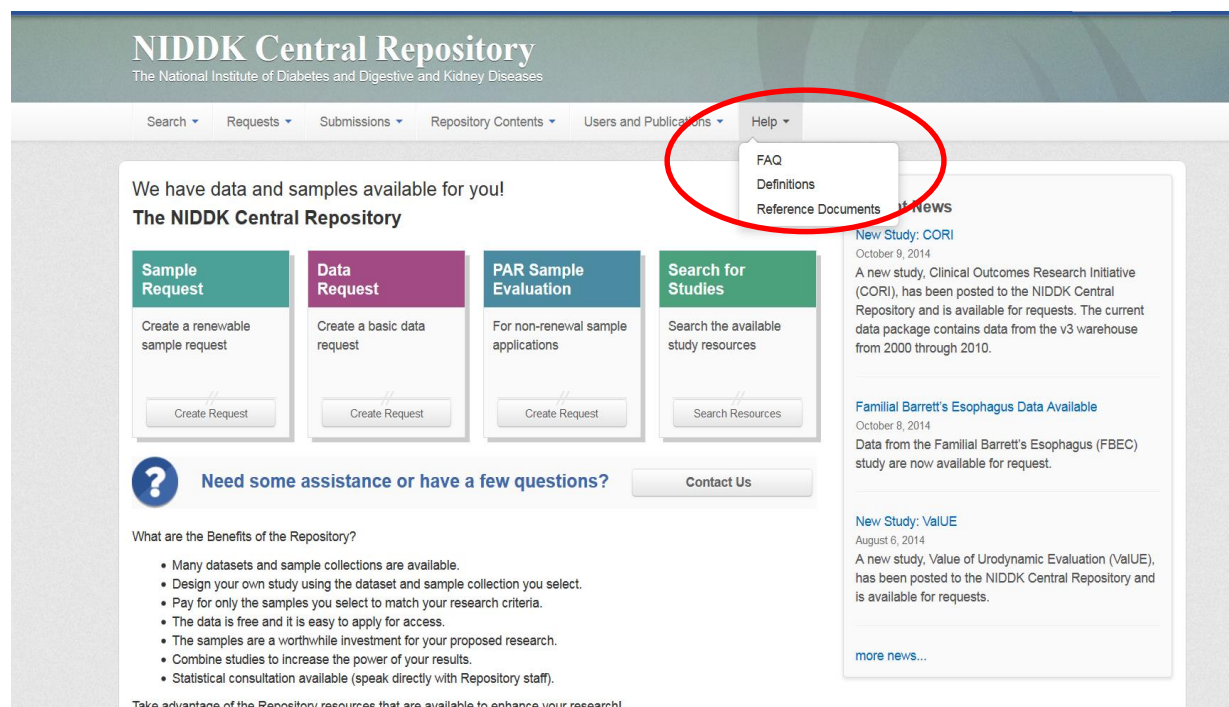
7) Once you receive the approval email, you can return to the website and log in by clicking on “Log in with your IMS Login Service account”. You will be then be asked to provide some additional information to finalize your account.

30.3.3 Download and Complete the Sample and Data Use Certification (SDUC)

Before submitting the online application, the PI must download the Sample and Data Use Agreement form, also referred to as **Sample and Data Use Certification (SDUC)**. The form requires authorized signatures from the PI’s institution and NIDDK Officials, and may take a few weeks to finalize and obtain the authorized signatures. Therefore, it is important to have the form completed before starting the online application process.

In order to download the Sample and Data Use Agreement Form:

1. Go to <https://www.niddkrepository.org>
2. Scroll over “Help” on the menu tab at the top of the page and choose “Reference Documents” from the drop-down menu.



- Click on “NIDDK Sample Data and Distribution Agreement (SDUC)” to download the Sample and Data Use Agreement.

NIDDK Central Repository
The National Institute of Diabetes and Digestive and Kidney Diseases

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Home > NIDDK Central Repository Documentation

NIDDK Central Repository Documentation

General Documentation

- [NIDDK Data Sharing Policy \(DOCX - 23KB\)](#)
- [Data and Sample Sharing Form \(DOCX - 15KB\)](#)
- [NIDDK Sample Data and Distribution Agreement \(SDUC\) \(PDF - 140KB\)](#)
- [NIDDK Data and Distribution Agreement \(DUC\) \(PDF - 145KB\)](#)

Data and/or Biospecimen Request Documentation

- [Non-Renewable Sample Request Form](#)
- [Data Request Form](#)
- [Renewable Sample Request Form](#)
- [Ancillary Request Form](#)
- [Internal Request Form](#)

If you need help accessing information in different file formats such as PDF, XLS, DOC, see [Instructions for Downloading Viewers and Players](#).

- Fill out the Sample and Data Use Agreement and have the completed form signed by your institution.

NIDDK Central Repositories
Sample and Data Use Agreement
Version date 01 December 2009
Contact: nid9k-daac@mail.nih.gov

Requestor: _____
E-mail Address: _____
Requesting Institution: _____
Requested Samples ("Samples"), including amounts: _____
Requested Dataset(s) ("Dataset(s)"): _____
If Requestor is funded by NIDDK for this Research Project, the NIDDK grant number is: _____

Introduction

The National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) has supported collection of Data and Samples from participants in numerous studies. In order to maximize the benefits of these resources collected with public funds and maximize their research value, it is important that these resources be made available, on appropriate terms and conditions, to the largest possible number of qualified investigators in a timely manner.

The NIDDK Central Database Repository does not receive personally identifiable information or codes linking such information to Samples or Dataset.

In the event that investigators from more than one institution will be collaborating on a project using the Samples or Dataset(s) transferred under this Agreement, an investigator from each institution is required to complete a separate Sample and Data Use Agreement request.

It is the intent of the NIDDK that Approved Users of NIDDK Central Repositories Samples and Dataset(s) recognize the limitations imposed by the original informed consent agreements of contributing studies as described on the NIDDK Central Repositories website.

Terms of Access:

1. Definitions:

Approved Users: Means research investigators who submitted a request for access to NIDDK Central Repositories Samples and Dataset(s) that have been approved by the NIDDK Data Access Committee and who have a fully-executed Sample and Data Use Agreement for the requested Samples and Dataset(s).

Contributing Study Investigators: Means research investigators who provided the phenotypic data and samples to the NIDDK Central Repositories.

Research Project: Attached as Appendix A, includes the project title, the Requestor's name and Requesting Institution's name, the names of any independent collaborators and their institutions.

NATIONAL INSTITUTE OF
DIABETES AND DIGESTIVE AND
KIDNEY DISEASES

NIDDK Repositories
Sample and Data Use Agreement Confidential Page 1 of 8

Authorized Signature for Requesting Institution
Name of Authorized Signatory: _____
Title of Authorized Signatory: _____

NIDDK INFORMATION and AUTHORIZED SIGNATURE

Program Official: _____ Date: _____
Rebekah Rasooly, PhD, KUH
National Institute of Diabetes and Digestive and Kidney Diseases

Authorized Signature _____ Date: _____

Name of Authorized Official: Cindy Fuchs, JD
Title of Authorized Official: Director, Office of Technology Transfer and Development
Address: 6707 Democracy Blvd., Rm. 778
Bethesda, MD 20817

Any false or misleading statements made, presented, or submitted to the Government, including any relevant omissions, under this Agreement and during the course of negotiation of this Agreement are subject to all applicable civil and criminal statutes including Federal statutes: 31 U.S.C. §§ 3801-3812 (civil liability) and 18 U.S.C. § 1001 (criminal liability including fine(s) and/or imprisonment).

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KIDNEY DISEASES

NIDDK Repositories
Sample and Data Use Agreement Confidential Page 7 of 8

30.4 UPLOADING ONLINE SAMPLE REQUEST APPLICATION

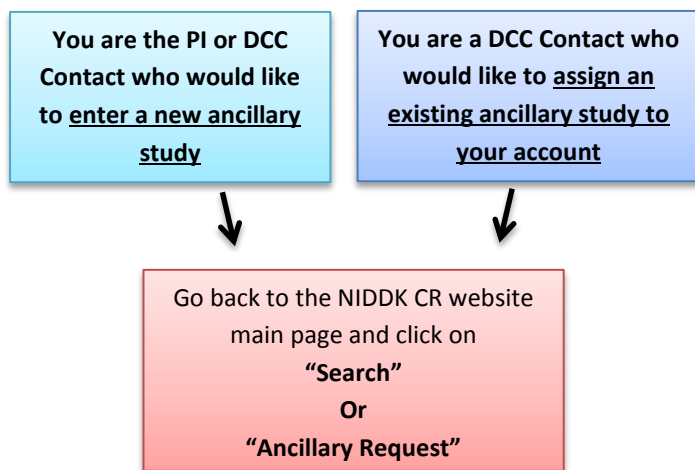
After the PI has emailed the Request Checklist form to the DCC, obtained the DCC approval letter, obtained IRB approval, and completed the SDUC (Sample and Data Use Agreement) with all authorized signatures, then the PI will be ready to submit the NIDDK online sample request application.

To upload the online application, the PI must:

1. Determine whether the ancillary study is either:
 - A New Ancillary Study
 - Choose from a list of Existing CKiD Ancillary Studies
2. Complete the online sample request form

30.4.1 Requesting Repository Samples via Search or by selecting Ancillary Request

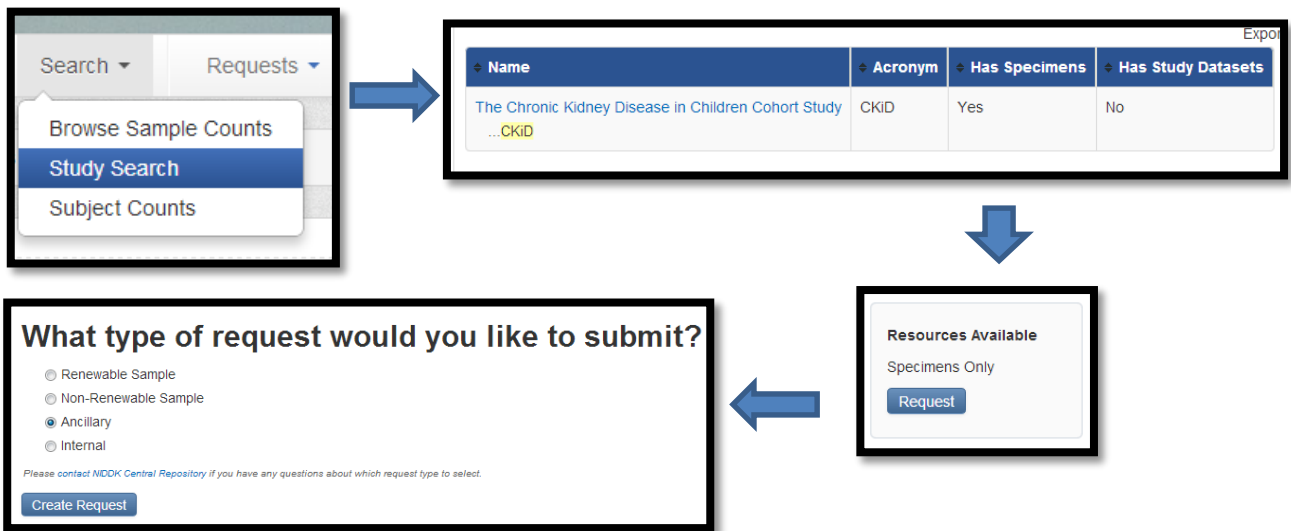
Request for repository samples can be initiated by performing “Search” or by selecting “Ancillary Request”. Either will option take you to the “Ancillary Request Form” web page. Use the following guidelines to determine your next step:



30.4.1.1 Submit request via “Search”

Requests on the NIDDK repository website can be initiated through search. On the main page, scroll over to search and click on “Study Search” on the drop down menu. They search for The CKiD study.

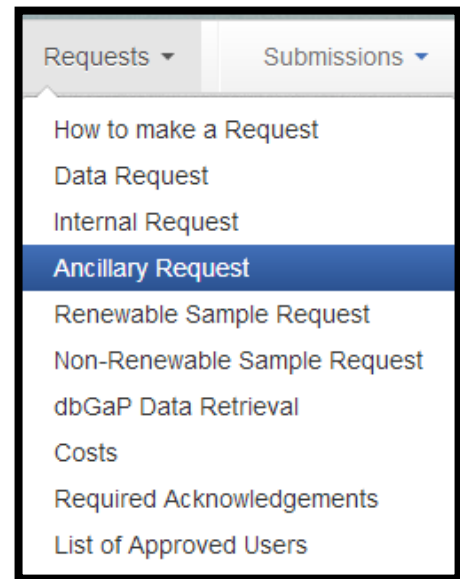
1. Login to the NIDDK repository website.
2. Scroll over “Search” on the menu tab at the top of the page and choose “Study Search” from the drop-down menu.
3. Type in “The CKiD Study” in the search box. Click on the CKiD study link to go to the study page.
4. From the CKiD study page, click on “Request”
5. Click on “Ancillary” and click “Create Request”



30.4.1.2 Submit request via “Ancillary Request”

Requests on the NIDDK repository website can be initiated by selecting “Ancillary Request”.

1. Login to the NIDDK repository website.
2. Scroll over “Request” on the menu tab at the top of the page and choose “Ancillary Request” from the drop-down menu.

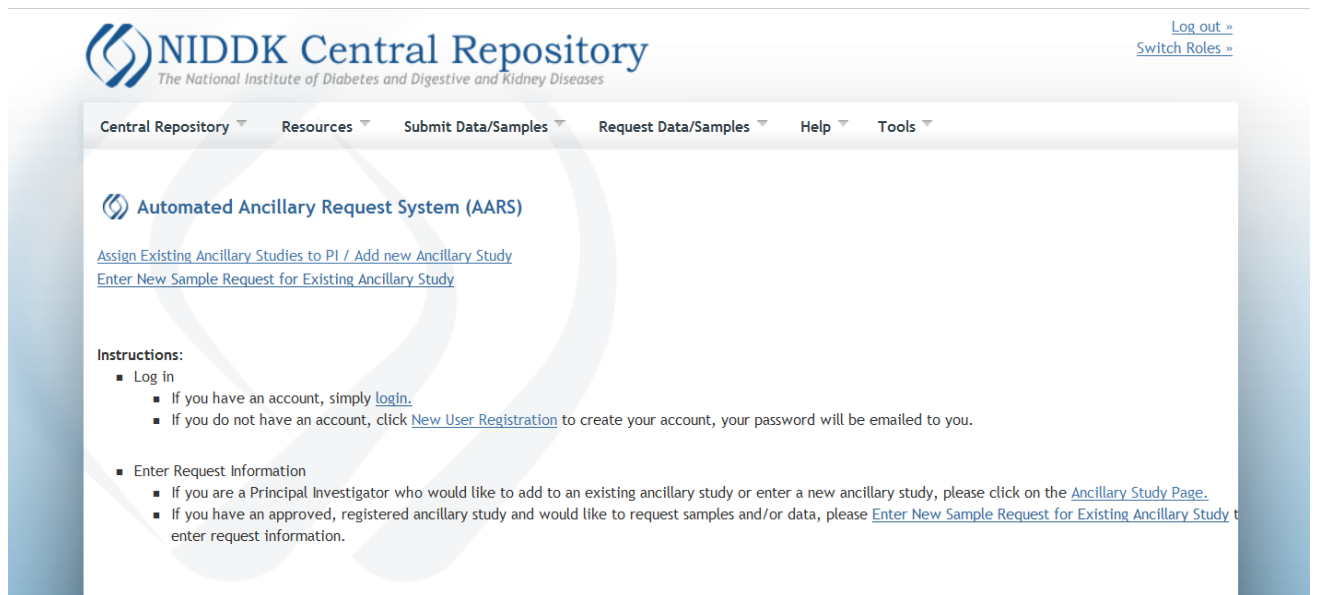


30.4.2 Completing the Online Ancillary Request Form

When the PI is ready to complete the online sample request, the following files should be saved in PDF format so that they can be uploaded.

- DCC approval letter
- Completed SDUC (Sample and Data Use Agreement) with all authorized signatures
 - Institution’s IRB approval letter (the IRB approval letter should be attached at the end of the SDUC)

All fields marked with an asterisk (*) are required. Fill out the form according to the following instructions (each step is annotated on the form template pictured below):



1. Input your request's nickname.
2. Select your original request if this is a continuation of a previous request (e.g., subsequent shipment).
3. Confirm and complete requestor/PI information. Fields initially auto-populated from your profile but is editable.
 - Name, address, title, phone numbers, email address and website information of the Principal Investigator (PI) of the ancillary study.
4. Enter the grant number and/or support type for PI's research.

NIDDK Central Repository

The National Institute of Diabetes and Digestive and Kidney Diseases

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Home > My Requests > Ancillary Request

Ancillary Request Form

If you are interested in requesting samples from a specific collection stored at the NIDDK Repository, update and submit the form below and a member of the NIDDK Central Repository staff will contact you within 7-10 days. If desired, you may save the form instead and return to complete it at a later time.

** Required Field

Ancillary Request

Request Name*

Create a nickname for your reference

1

Request Lineage

Originating Request

2

Requestor Information

<p style="font-size: x-small; margin: 0;">Name*</p> <input style="width: 95%; border: 1px solid #ccc;" type="text"/>	<p style="font-size: x-small; margin: 0;">Address*</p> <input style="width: 95%; height: 30px; border: 1px solid #ccc;" type="text"/>
<p style="font-size: x-small; margin: 0;">Email*</p> <input style="width: 95%; border: 1px solid #ccc;" type="text"/>	<p style="font-size: x-small; margin: 0;">Institution</p> <input style="width: 95%; border: 1px solid #ccc;" type="text"/>
<p style="font-size: x-small; margin: 0;">Title</p> <input style="width: 95%; border: 1px solid #ccc;" type="text"/>	<p style="font-size: x-small; margin: 0;">Fax</p> <input style="width: 95%; border: 1px solid #ccc;" type="text"/>
<p style="font-size: x-small; margin: 0;">Phone</p> <input style="width: 95%; border: 1px solid #ccc;" type="text"/>	<p style="font-size: x-small; margin: 0;">PI Name</p> <input style="width: 95%; border: 1px solid #ccc;" type="text"/>
<p style="font-size: x-small; margin: 0;">Website</p> <input style="width: 95%; border: 1px solid #ccc;" type="text"/>	

A URL for the requestor if they have a site

Support Information

Grant

4

5. Enter shipping information.
6. Select CKiD, if it is not already selected.
7. Select your Ancillary Study name, if it appears. If it does not appear, leave blank.
8. Enter the basic details of your request including the number and type of specimen as well as brief description (such as an executive summary).
9. Enter any comments (e.g., shipping instructions)
10. Select the appropriate option for data sharing questions.

11. Attach the documents. Do the following to attach documents:

- Click the ‘Choose File’ button
- Navigate to the desired file and select it using the dialog that appears. Click ‘Open’, and the file's location on your computer will appear in the ‘Choose file’ box.
- If desired, enter a file description in the ‘Optional Description of file’ control.
- Check any boxes in the ‘Requirements Fulfilled’ section that describe the purpose or function of the file.
- Click the ‘Attach’ button, and the file will appear in the ‘Attached Files’ list on the right side of the page .

12. Click “Submit” to send your request to NIDDK CR staff.
Or click “Save for Later”. “Save for Later” allows you to complete the request at another time (via the My Requests page). Save request are not visible to NIDDK CR staff.

30.5 COMMENTS TAB

Once the request is submitted all communication with repository staff should be done through your request on the NIDDK Central Repository website.

To return to your request:

- click on 'My Requests'
- click on the request ID

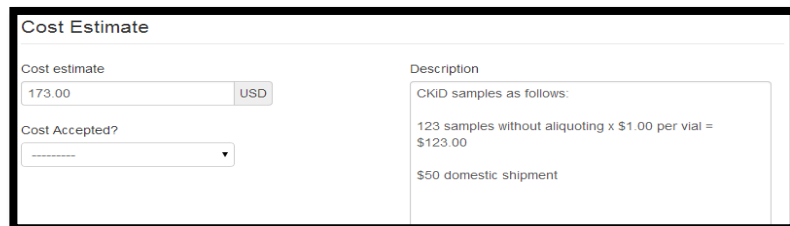
Use the comments tab to send a message to NIDDK CR staff. You can also attach any relevant documents. The attachment will not be submitted until you click both 'Attach' and then 'Update Request.'

This tab also displays a history of all previous comments made by the requestor or NIDDK CR staff. You are notified if any issues arise with your sample request. If no problems are encountered, you will be notified when your samples are ready for shipping.

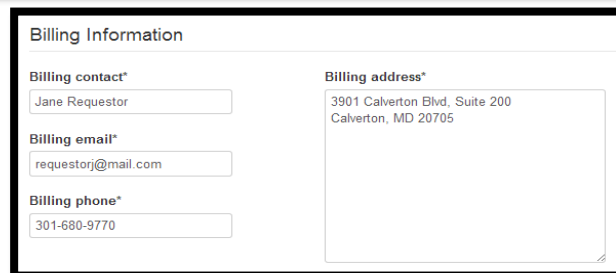
30.6 COST TRACKING TAB

The cost tracking tab displays the cost estimate and billing contact information.

- You will receive notification once the cost estimate is ready to be viewed on the cost tracking tab.
- You accept the cost using the dropdown menu located next to the description and under the dollar amount.
- Billing contact information must be entered at this time as well.
- Cost estimates over \$5000 require payment prior to specimen processing.



The screenshot shows a 'Cost Estimate' form. On the left, there is a 'Cost estimate' field with the value '173.00' and a 'USD' currency selector. Below it is a 'Cost Accepted?' dropdown menu. On the right, there is a 'Description' field containing the text: 'CKiD samples as follows: 123 samples without aliquoting x \$1.00 per vial = \$123.00 \$50 domestic shipment'.



The screenshot shows a 'Billing Information' form. It has two columns. The left column contains three fields: 'Billing contact*' with the value 'Jane Requestor', 'Billing email*' with the value 'requestor@mail.com', and 'Billing phone*' with the value '301-680-9770'. The right column contains a 'Billing address*' field with the value '3901 Calverton Blvd, Suite 200 Calverton, MD 20705'.

30.7 QUESTIONS AND CONTACTS

If you have any questions regarding the process for requesting samples or need further information, please use the following contact information below.

NIDDK Central Repository
c/o Information Management Services

Phone: (301) 680-9770
E-mail: niddk-cr@ims.web.com

Judith Jerry-Fluker
KIDMAC Project Director
CKiD Data Coordinating Center

Phone: (410) 614-1277
E-mail: jjerry@jhu.edu

30.8 AFTER THE ONLINE APPLICATION IS UPLOADED

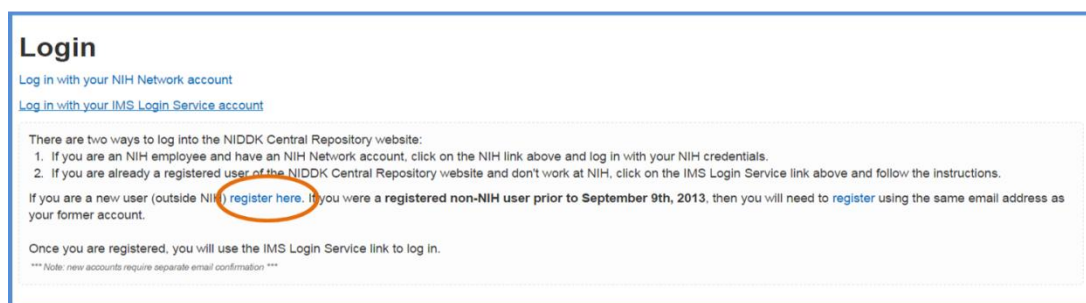
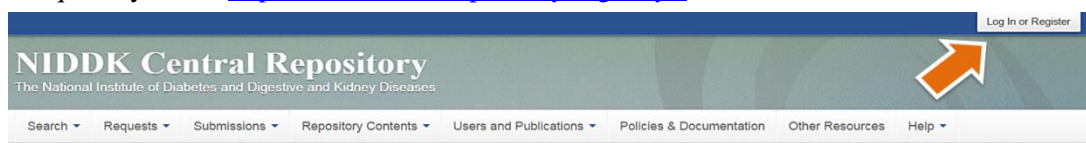
The PI must notify the DCC that a complete application has been submitted. Once notification is received, the DCC will email the PI the list of samples to ship based on the information contained in the Request Checklist Form. The PI must upload the list of samples on the website. Although not preferable, the PI can also ask the DCC to upload the list of samples on the NIDDK website.

30.9 REQUESTING PUBLIC DATA

Investigators interested in receiving publically archived CKiD data can make their request directly to the NIDDK Data Repository, the Information Management Services (IMS). The following sections outline the steps in making a request to receive data. The steps are similar to making a sample request; however, there differences. Therefore, investigators should read the steps carefully and contact IMS via email at niddk-cr@imsweb.com to address questions or problems.

30.9.1 Before making a data request, you must complete two steps:

1. Obtain documented Institutional Review Board (IRB) approval or exemption from your institution.
2. Registers for a user account on the NIDDK website so you can access and use the data request systems: <https://www.niddkrepository.org/wayf/>



IMS Login Service

Apply For A New Account

Your new account can be used to log into participating portals and web applications that use the IMS Login Service. Please [contact us](#) if you have questions about the process.

All fields are required.

Profile Information

First Name:

Last Name:

Email Address:

If you were invited to create an account by another system, please make sure to use the email address that received the invitation.

Verify Email Address:

Phone Number:

Used for account verification.

Choose a Username

At least 3 characters long.
Letters and numbers only.

Username:

Usernames are case-sensitive.
Recommend using one that's easy to remember such as a combination of your last name and first initial.

Choose a Password

Passwords must be at least 8 characters long and include characters from at least 3 of the following:

- Uppercase letters (A-Z)
- Lowercase letters (a-z)
- Numerals (0-9)
- Special characters (! # \$ % & * + = , - . / : ; () < > ? @ \ ^ _ ' ~)

Passwords will expire every 60 days.


30.9.2 Online Data Request Process

Making the data request online:

1. Login with your registered user account information

Login

Log in with your NIH Network account

Log in with your IMS Login Service account 

There are two ways to log into the NIDDK Central Repository website:

1. If you are an NIH employee and have an NIH Network account, click on the NIH link above and log in with your NIH credentials.
2. If you are already a registered user of the NIDDK Central Repository website and don't work at NIH, click on the IMS Login Service link above and follow the instructions.

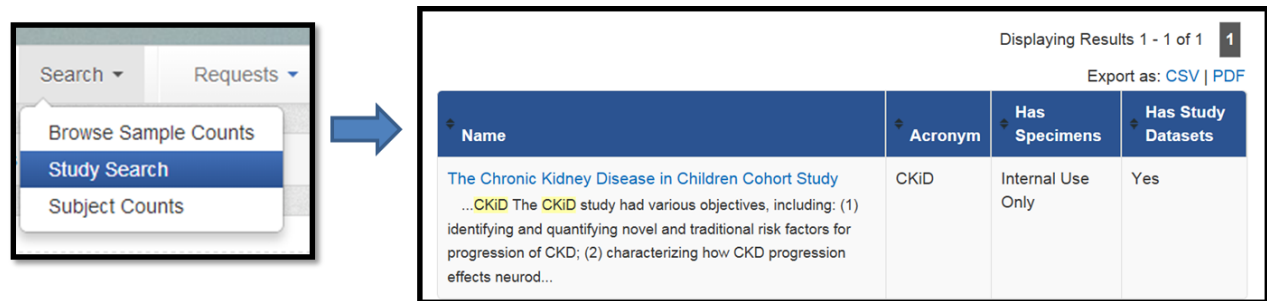
If you are a new user (outside NIH) [register here](#). If you were a **registered non-NIH user prior to September 9th, 2013**, then you will need to register using the same email address as your former account.

Once you are registered, you will use the IMS Login Service link to log in.

*** Note: new accounts require separate email confirmation ***

2. Access the CKiD study page on the NIDDK repository website via:

a. The 'Study Search' tool

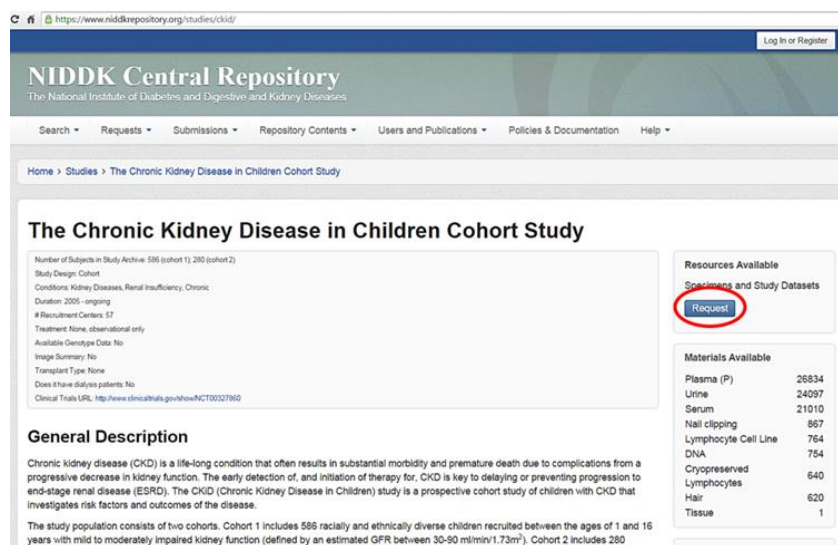


The screenshot shows the 'Study Search' tool on the left, with a dropdown menu open showing 'Study Search' selected. An arrow points to the search results on the right. The results table shows one result for 'The Chronic Kidney Disease in Children Cohort Study' (CKiD).

Name	Acronym	Has Specimens	Has Study Datasets
The Chronic Kidney Disease in Children Cohort Study ...CKiD The CKiD study had various objectives, including: (1) identifying and quantifying novel and traditional risk factors for progression of CKD; (2) characterizing how CKD progression effects neurod...	CKiD	Internal Use Only	Yes

b. The direct link to the CKiD study page: <https://www.niddkrepository.org/studies/ckid/>

3. Click "Request" on the CKiD study page:




The screenshot shows the CKiD study page. The 'Request' button is circled in red. The page includes a 'Resources Available' section with a table of specimens and study datasets.

Resources Available	Specimens and Study Datasets
Request	

Materials Available	
Plasma (P)	26834
Urine	24097
Serum	21010
Nail clipping	867
Lymphocyte Cell Line	764
DNA	754
Cryopreserved Lymphocytes	640
Hair	620
Tissue	1

4. Select “data” as type of request; click “Create Request”:

What type of request would you like to submit?

Data 

Ancillary

Internal

Please contact NIDDK Central Repository if you have any questions about which request type to select.

5. Complete the Data Request Form online

Data Request Form

If you are interested in requesting specific collection data from the NIDDK data repository, update and submit the form below and a member of the contact you within 7-10 days. If desired, you may save the form instead and return to complete it at a later time.

* = Required Field

Data Request

Request Name* 1. Input your request’s nickname.

Create a nickname for your reference

Requestor Information 2. Confirm and complete requestor information. Fields initially autofilled from your profile but editable.

<p>Name*</p> <input type="text" value="Lynn Pereira"/>	<p>Address</p> <input type="text" value="615 N. Wolfe St E7010 Baltimore MD 21205 USA"/>
<p>Email*</p> <input type="text" value="lpereira@jhu.edu"/>	
<p>Title</p> <input type="text"/>	<p>Institution</p> <input type="text" value="Johns Hopkins University"/>
<p>Phone</p> <input type="text" value="410-502-2755"/>	<p>Fax</p> <input type="text"/>
<p>Website</p> <input type="text"/>	
<p><small>A URL for the requestor if they have a site.</small></p>	
<p>PI Name*</p> <input type="text"/>	<p>PI Institution*</p> <input type="text"/>
<p>PI Email*</p> <input type="text"/>	

Support Information 3. Enter the grant number and/or support type for your research.

<p>Support Type</p> <input type="text" value=""/>	<p>Other</p> <input type="text"/>
<p>Grant/PAR Number</p> <input type="text"/>	

Request Details

Study* **6. Select CKiD as the study if not already selected.**

Select the desired studies.

Information Security: Please check the information security practices to be used

- Institute supported, controlled access server
- Institute supported, password protected desktop computer
- Encrypted, password protected laptop computer
- Encrypted portable media (encrypted external hard drive, encrypted thumb drive)
- Unencrypted portable media backup (CD, DVD, thumb drive) stored in locked file cabinet

5. Provide the details of the "information security practices" to be used.

Study data must be maintained in a secure and controlled environment

Comments

Agreement Form **4. Provide information about your research plan in the Agreement Form section.**

Title of Research Plan*

Other Users*

Collaborators

Names of any independent collaborators and their institution(s)

Requested Materials*

Description of Research*

Research Objectives and Design*

Attachments 7. Attach the appropriate documents (i.e. IRB approval letter)

Please submit any related attachments below. After selecting a file, please specify the requirements fulfilled by the attachment and then click on the "Attach" button. Optionally, you may also specify a file description. When you are done with all your changes, you must then click the "Update Request" button. For more assistance, you may view more complete [attachment instructions](#).

Select a file: No file chosen

Optional Description of file:

Attached Files

No files have been attached.

This File Fulfills:

Cost Invoice

IRB Approval

8. Click "Submit" to send your request to NIDDK CR staff.
"Save for Later" allows you to complete the request at another time (via the My Requests page). Saved requests are not visible to NIDDK CR staff.

30.9.3 Data Use Certification (DUC) Form

Once the request is submitted, repository staff will review the information submitted and provide a Data Use Certification (DUC) agreement for signature. This agreement includes an appendix for outline of the intended Research Project and requires authorized signatures from the study PI and institution. If collaborating with external investigators, an investigator from each institution is required to complete a separate Data Use Certification Agreement request.

A copy signed by NIDDK officials is returned to the investigator via the NIDDK's website request portal shortly after fulfillment. Data access is granted for one-year from the date of the Data Use Certification approval. Renewal of access may be granted by submitting a request to the NIDDK Central Repository.

30.9.4 Public Dataset

After the appropriate signatures are obtained and the PI obtains a fully-executed Data Use Certification agreement, the data repository will provide the investigator with a link to download the data package. The link is valid for six months. The data package will include all of the baseline and follow-up data collected as of 2013, as well as all data and study documentation. The data will be in the form of SAS datasets, with copies in CSV.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 31: CARDIAC MAGNETIC RESONANCE IMAGING (MRI)

31.1 INTRODUCTION

Cardiac magnetic resonance imaging (MRI) will be implemented in order to assess heart disease and conditions in children with a high probability of reaching end-stage renal disease (ESRD). Cardiac MRIs will be performed only on a sub-set of the cohort who are eight (8) years old or older. The cardiac MRI will be performed at whichever of the following visits occurs first:

- the first study visit after a participant reaches an estimated GFR (eGFR) ≤ 30 ml/min/1.73m².
 - The eGFR ≤ 30 eligibility threshold can be determined based on laboratory measurements (i.e., serum creatinine, BUN, cystatin C) obtained at whichever visit occurs first:
 - CKiD study visit, where serum samples are analyzed centrally at the Central Biochemistry Laboratory or
 - clinical visit, where serum samples are analyzed locally*
 - *Given that locally measured laboratory values are permitted for establishing cMRI eligibility, sites should consider determining eligibility prior to the CKiD visit to facilitate scheduling.
- an irregular visit prior to the initiation of renal replacement therapy (RRT)

The Cincinnati Children's Medical Center Cardiac MRI Center jointly run by the Heart Institute and the Diagnostic Radiology department will serve as the Cardiac MRI Coordinating Center (Cardiac MRI Center) for the CKIDS study. This protocol is a NHLBI funded multicenter observational study to comprehensively characterize the cardiac response to chronic kidney disease. Each participant will be asked to undergo a research-only cardiac MRI study without contrast material. MRIs must be completed in accordance with the procedures listed below. MRIs may be completed using a 1.5T or 3.0T scanner, although scans completed on a 1.5T scanner are preferred. The need for deep sedation, general anesthesia, or anxiolytics is not permitted.

31.2 GENERAL OVERVIEW

The cardiac MRI study is designed to evaluate the cardiac structure, chamber sizes, systolic and diastolic function, and ventricular mass. This protocol includes the following sections.

1. Localizers: Scout images to position the patient in the isocenter of the magnetic field.
2. Cine images: Cine images acquired in the short-axis plane from the base (atria) to the apex, using the SSFP sequence. Long-axis SSFP cine images are also acquired in the four-chamber, two-chamber, and three-chamber view.
3. Tagging: Line tagging performed in the vertical and horizontal direction. This series of images assesses the movement and strain of the myocardium. Three images are obtained at the base, mid and apex.
4. T1 map: These images are used to measure T1 value of the myocardium. On Siemens and Philips scanners, MOLLI (Modified Look Locker Inversion Recovery) or shMOLLI is used. On GE scanners, MLLSR (Modified Look Locker with Saturation Recovery) is

used. Three short axis slices are acquired at the base, mid, and apical tagging slice positions. Inability to acquire T1 maps will not exclude sites from participating.

5. Parallel imaging: All 2D sequences (SSFP and GRE) will use parallel imaging with an acceleration factor of 2.
6. 3T specific sequence: At 3T, SSFP cine imaging is vulnerable to artifacts from the off-resonance effect and RF non-uniformity. Additional shimming and frequency scouting is needed for high quality SSFP image at 3T.
7. Breath-holding: If the patient can reliably hold breath at resting lung volume, the study should be attempted with breath holds. If during patient orientation, it is determined breath holding is not possible, the cine imaging should be done free-breathing with 3-4 Nex (signal averages).

Sites are required to complete an MR form for each patient. Steps for image acquisition and the MR sequence parameters for the protocol are given below.

31.3 ABBREVIATIONS

BH:	Breath hold
CMRI:	Cardiac magnetic resonance imaging
ECG:	Electrocardiography
GRE:	Gradient recalled echo
HLA:	Horizontal long axis
IR:	Inversion recovery
MOLLI:	Modified Look Locker Inversion Recovery
MLLSR:	Modified Look Locker with Saturation Recovery
MRI:	Magnetic resonance imaging
NBH:	Non breath hold
SSFP:	Steady state free precession
TSE:	Turbo spin echo
VLA:	Ventricular long axis

31.4 SEQUENCE NAMING STANDARD

Please name the sequences on the scanner according to the left column, the right column is for your information.

Name

SCOUT	(three plane scout)
PVLA_SCOUT	(pseudo-vertical long axis scout)
SA_SCOUT	(short axis scout – 3 slices)
4CH_CINE	(horizontal long axis / four-chamber cine)
2CH_CINE	(vertical long axis / two-chamber cine)
SA_CINE_STACK	(short axis cine stack)
3CH_CINE	(three-chamber cine)
SA_TAGS	(short axis tagged stack – 3)
T1_MAP	(T1 map)
PC_AORTA	(Phase contrast of the ascending aorta)

31.5 PATIENT PREPARATION

- Complete the MRI safety screening form of your MRI center.
- Request that the patient use the restroom before the study
- Breath-holding is done at resting lung volume (exhalation) for the entire protocol.
- Inform and train the participant on breath-holding, for example: “Breathe in ... Let air out until you are comfortable, and then stop breathing.” If unable to hold breath the study should be performed free-breathing.
- Make sure that the connectors for cardiac coils and ECG are in place.
- Thoroughly clean the ECG contact area with alcohol wipe. With patient supine on the scanner table, attach ECG electrodes to his/her chest according to your MRI manufacturer suggestion.

31.6 CMR PROTOCOL

Please complete the MRI safety screening form of your center. The MRI data form should be started at the time of the exam. The time of study and any adverse events should be noted.

31.6.1 Multi-Planar Scout

The first multi-plane localizer acquired either free breathing or with breath hold to move the heart to the isocenter of the magnet. Three planes shown in figure 1.

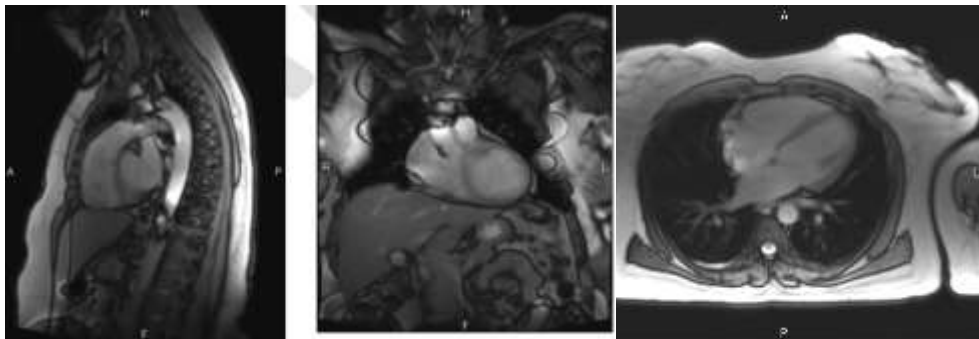


Figure 1. Three plane localizer

31.6.2 Axial SSFP of the chest.

This is a stack of non-ECG gated axial SSFP of the chest from the diaphragm to the thoracic inlet (Figure 2). This should be performed at resting lung volume if possible. Slice thickness 8mm and pixels < 2x2 mm.

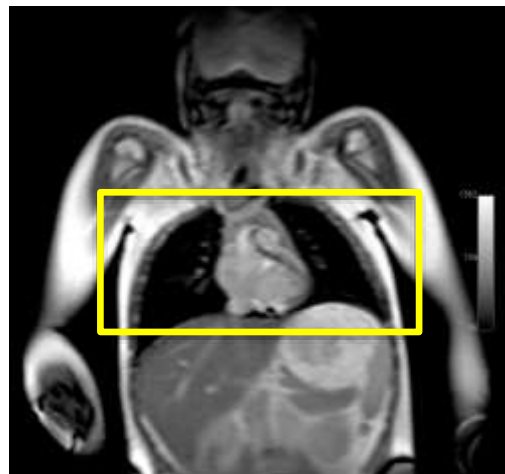


Figure 2. Anatomic plan for axial SSFP of the chest.

31.6.3 Cine imaging

Cine images will be acquired in the 2-chamber (vertical long axis), 4-chamber (horizontal long axis), 3-chamber, and short axis planes. The short axis acquisition will be stacks covering the entire heart including the atria. The acquisition will be a breath-hold at resting lung volume with retrospective gating. Absolute temporal resolution should be between 30-45 ms reconstructed to 30 phases. Spatial resolution should be $2 \times 2 \text{ mm}^2$ or smaller with slice thickness of $< 8 \text{ mm}$. The acquisition planes can be prescribed using the standard site specific protocol. For reference, an example of acquiring the planes is given below.

- A. **Pseudo vertical long axis** (Figure 3): Prescribe this using the axial scout view with the largest volume of heart, from the base (middle of the mitral valve) to apex of the left ventricle.

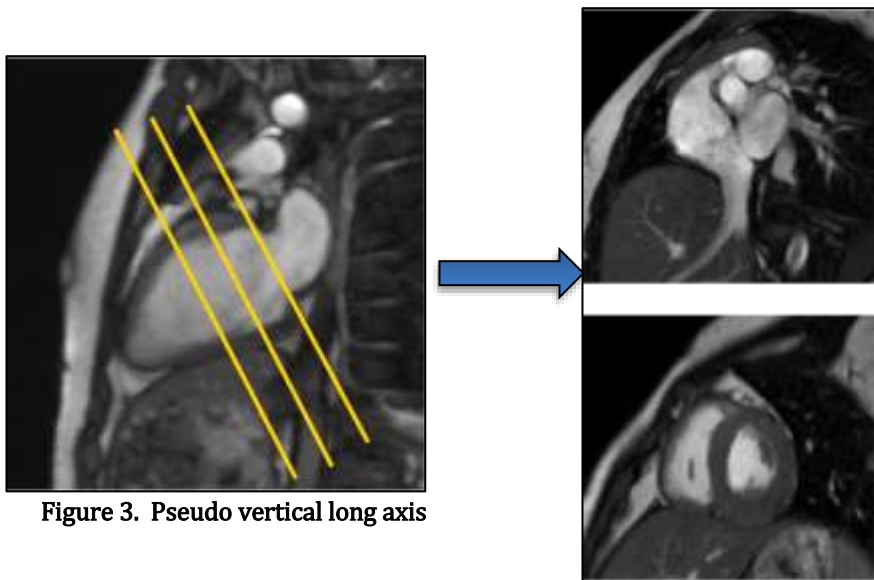


Figure 3. Pseudo vertical long axis

- B. **Short axis scout** (Figure 4): Prescribe 3 slices using the pseudo vertical long axis scout view parallel to the mitral valve plane. These will be used to plan the 4-chamber plane.

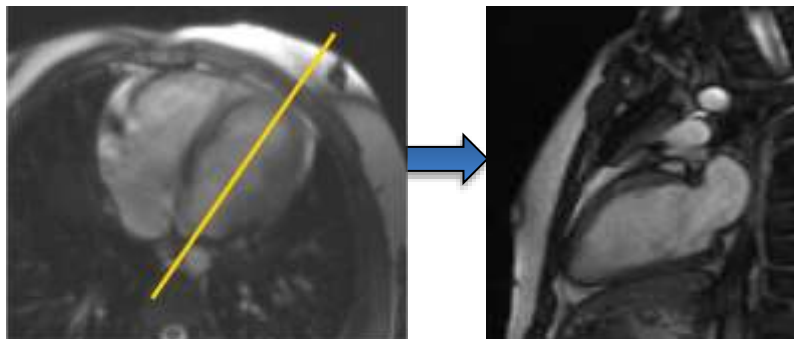


Figure 4. Three short axis scout slices planned on the pseudo long axis

- C. **4-chamber cine** (Figure 5): Prescribe 1 slice using the pseudo long and short axis scout planes for reference. The slice should go through the apex of the heart.

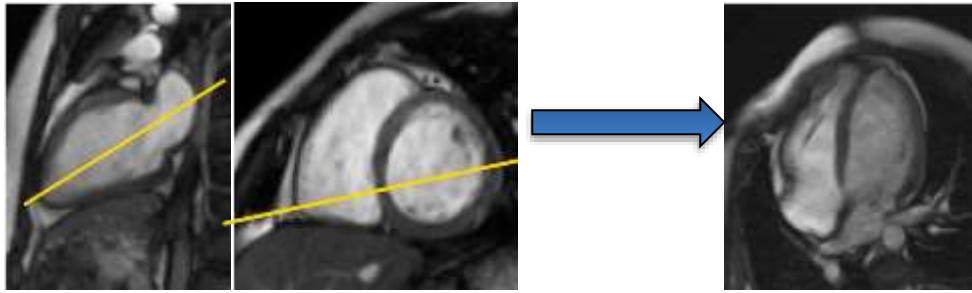


Figure 5. 4-chamber plane planned from the pseudo vertical long axis and a basal short axis scout slice. The plan can be checked on the other two sort axis scout slices.

- D. **2-chamber cine** (Figure 6): Prescribe 1 slice using pseudo-short axis mid-ventricular slice and the 4 chamber slice.

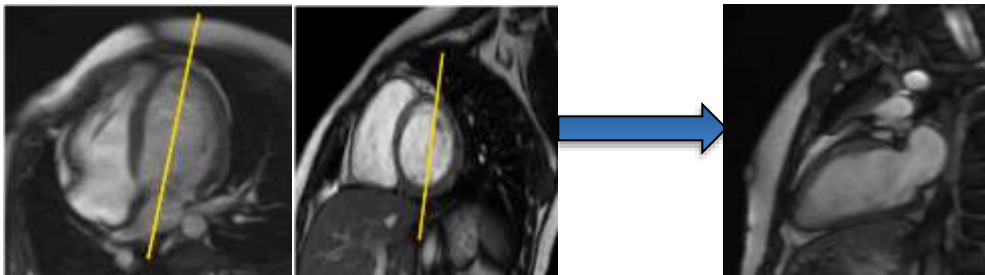


Figure 6. 2-chamber plane planned from the 4-chamber and short axis scout planes.

- E. **Short axis cine stack** (Figure 7): Prescribe 12-16 slices covering the entire left atrium and ventricle. The stack should be parallel to the mitral valve plane. Absolute temporal resolution ($TR \times$ views per segment) between 35-45ms and reconstructed to 30 phases. Slices should be set in descending order from base to apex. The first slice must begin superoposterior to the left atrial wall. Flip angle should be set at the largest possible, usually around 70 degrees(1.5T), although this depends on the MRI manufacturer.

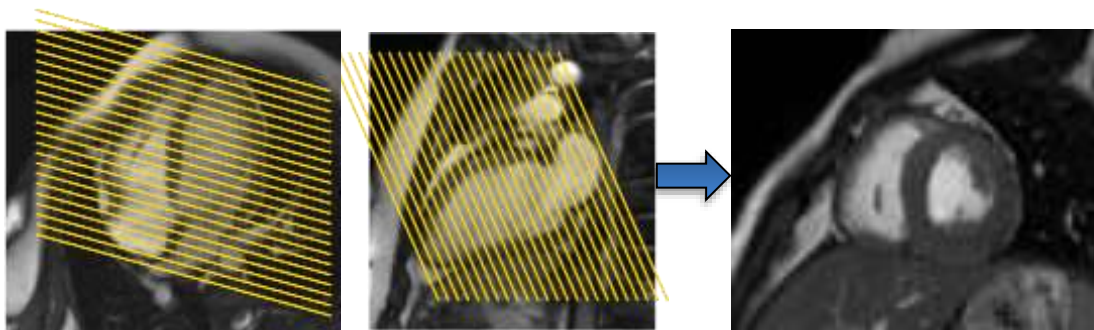


Figure 7. Short axis stack of slice covering the entire left atrium and ventricle.

- F. **Three-chamber cine** (Figure 8): Prescribe one 3 chamber slice using the basal short axis slice at the aortic valve level and the two-chamber plane. (the echocardiographic corollary is the parasternal long axis view).



Figure 8. 3-chamber plane planned from the short axis and 2-chamber planes. The plan can also be checked on the coronal localizer.

31.6.4 Tagged imaging

These are bright blood (FGRE) images with magnetic saturation bands. Tagged images will be acquired in three short axis planes, 4-chamber, and 2-chamber planes. Slice thickness of 8 mm and pixel dimensions no bigger than 2x2 mm. A single 4-chamber and 2-chamber slice is acquired using the same planning procedure as used for the cine imaging (Figure 9).

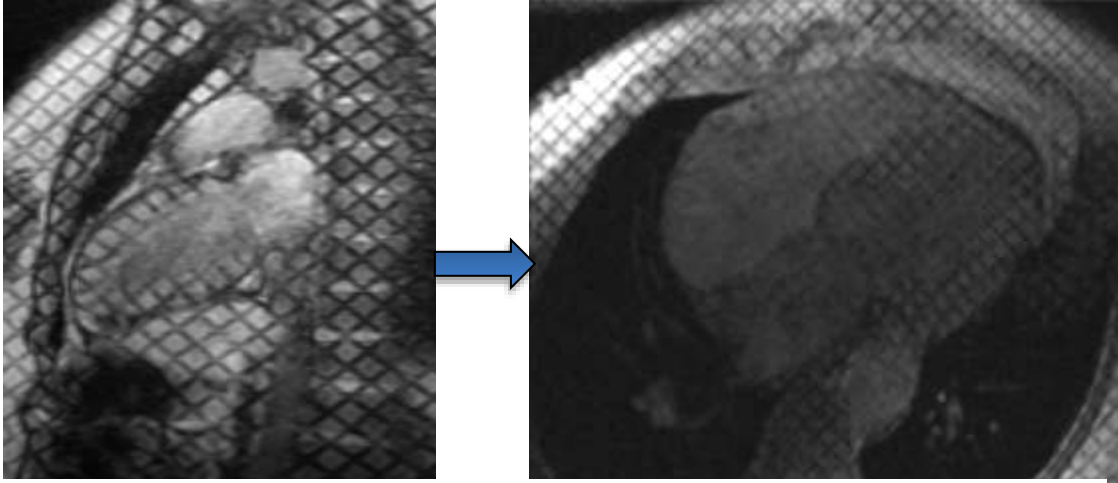


Figure 9. 2-chamber and 4-chamber grids shown at the beginning of systole. The tags will fade during mid to late diastole.

For the short axis slices (Figure 10), the upper slice should be placed at the level of mitral valve IN SYSTOLE and the slice spacing adjusted so the third slice is just above the apex. Prospective gating should be used with 20-26 phases. Images should be acquired at resting lung volume. The preferred tag spacing is ≤ 7 mm.

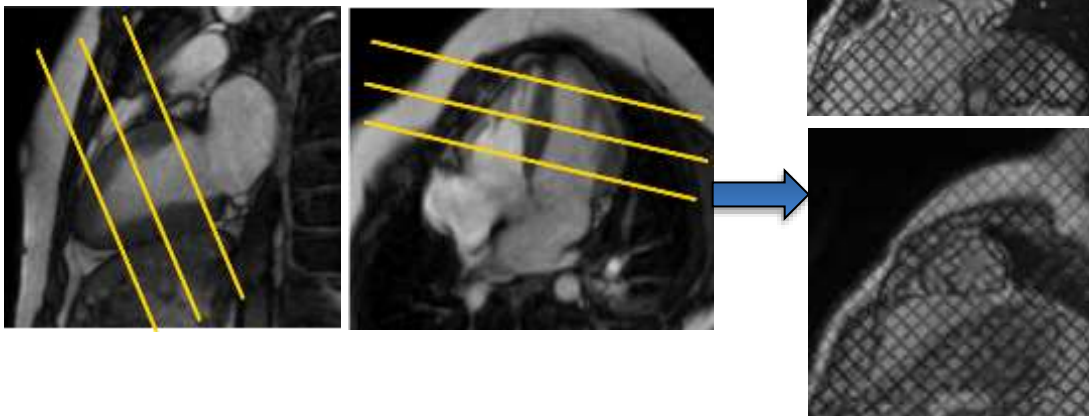


Figure 10. Short axis slices with grids planned from the 2- and 4- chamber slices in systole.

31.6.5 Phase contrast velocity imaging

Free breathing velocity images of the aorta and the atrioventricular valves will be acquired. Phase contrast (PC) images will be obtained using ECG-gated velocity-encoded cine sequences during free breathing. Acquisition parameters include: retrospective gating; FOV: maximum; slice thickness: 6 mm; in-plane resolution: adjusted to minimum of 16 voxels in ROI; calculated phases per cardiac cycle: 30

calculated phases (for high heart rates, reduce phases to keep phase percentage >50%); parallel imaging ≤ 2 ; NEX = 3 or greater.

The aortic plane (Figure 11) should be adjusted to be perpendicular to the proximal ascending aorta ~2-5 mm distal to the sinotubular junction. The VENC should be set to 200 m/s.

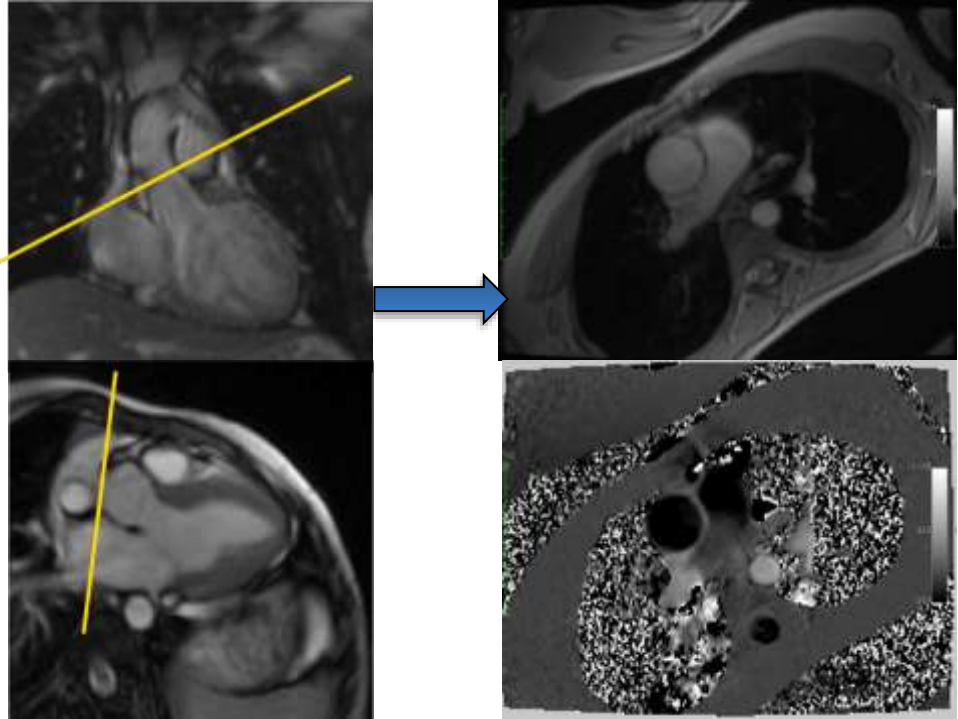


Figure 11. Left panel: Coronal localizer and 3-chamber cine used to plan the aortic PC. Right panel: The magnitude and phase image of the aorta.

For the atrioventricular valves, the plane should be prescribed using both the 4-chamber and the 2-chamber views in systole (Figure 12). The plane should extend across both the tricuspid and mitral valves in systole. The VENC should be set to 100 m/s. If there is significant difficulty obtaining the mitral and tricuspid valves in the same plane, they should be acquired in separate acquisitions.



Figure 12. 4-chamber and 2-chamber planes used to plan the mitral and tricuspid valve PC slice.

31.6.6 T1 mapping

Three breath-held mid-ventricular short axis slices for T1 mapping should be acquired at the same location as the tagged images. On Siemens and Philips scanners, a MOLLI protocol will be used. The number of post-inversion echoes will vary according to the scanner. The standard MOLLI sequence on the Philips is 11 acquisitions. Base resolution should be set to 256, flip angle to 35 degrees.

31.7 ALERT FINDINGS

The MRI alert findings procedure is similar to that described for the echo protocol. The alert parameters include findings of congenital heart disease, intracardiac or intravascular vegetation, tumor, pericardial effusion and/or tamponade, left ventricular or atrial thrombus, or cardiomyopathy (hypertrophic/dilated). It is highly recommended that the local site screen all the exams for “Alert” findings. In the event that an alert is found by the local site, the local coordinator will contact the site PI. 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. In instances in which an “alert” parameter is identified by the core cardiac MRI laboratory (CCHMC), cardiac MRI center will contact the site PI.

31.8 QUALIFYING STUDY

Each participating site will be required to submit a qualifying study. The study can be either a volunteer or a clinical study that has been de-identified (absence of name, DOB, medical record/account number, etc.). Either 1.5 or 3T studies are acceptable, the study exams must be performed on the same magnet as the qualifying study. Each submitted qualifying study will be scored on a 5 point binary scale for

1. Protocol completeness
2. Appropriate parameters
3. Appropriate plan geometry
4. Image quality
5. Image adequacy for numerical analysis

A perfect score of 5 will allow admission into the study without changes. Any score of less than 5 will require discussion between the CCHMC cardiac MRI core PI and the performing site PI and / or cardiac MRI personnel to determine changes that need to be made to make the studies acceptable.

31.9 KEY OUTCOME PARAMETERS

Right and left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) stroke volume, ejection fraction and ventricular mass will be measured using semi-automate planimetry as implemented in standard commercially available software (MASS: Medis, Leiden, The Netherlands).

Ejection fraction will be calculated as $[(EDV-ESV)/EDV]$.

CI (L/min/m²) will be calculated as stroke volume (EDV-ESV) times heart rate in beats per minute, divided by body surface area (m²).

Net flow in the aorta, and forward flow in the mitral valve and tricuspid valve will be measured using commercial software (FLOW: Medis, Leiden, The Netherlands).

Both regional and global strain will be calculated.

Using the HARP (Diagnasoft; Cary, NC) technique, circumferential regional and global left ventricular systolic strain will be calculated at three levels (basal, mid, and apex).

31.10 DATA MANAGEMENT PLAN

31.10.1 MRI Data

All MRI images must be saved as unaltered anonymized DICOM data and should be sent via FedEx to:

Attn: Michael Taylor, MD, PhD
CKID MRI data
CCHMC
The Heart Institute, ML 2003
3333 Burnet Avenue
Cincinnati, OH 45229

➤ **Contact your CCC for a FedEx slip (if needed) and it will be emailed to you**

Data should be sent to CCHMC within two (2) weeks of study completion. We have set up a Dropbox account that will be used to accept DICOM data. It must be anonymized before being uploaded.

31.10.2 Quality assurance

The study coordinator at CCHMC will keep record of the data received and will distribute the data to the study-specific MRI specialists for analysis. Dr. Michael Taylor of Cincinnati Children's Hospital Medical Center and Dr. Tim Slesnick of Children's Healthcare of Atlanta will serve as the study-specific MRI specialists. 10% of all data will be selected at random to be read by both MRI specialists. If there is a greater than 5% difference in phase contrast values or a greater than 10% difference in volumetric values between the study-specific MRI specialists, the studies will be reviewed together.

31.11 QUESTIONS AND CONTACT

Dr. Michael Taylor is available to answer questions and assist with protocol implementation.

Michael Taylor, M.D., Ph.D.
Director, Advance Imaging Innovation
Assistant Professor, UC Department of Pediatrics
Cardiac MRI Coordinating Center
The Heart Institute
Cincinnati Children's Medical Center
3333 Burnet Ave
Cincinnati, OH 45229
Telephone: 513-803-0426
E-mail: michael.taylor1@cchmc.org

31.12 CARDIAC MRI FORM

Chronic Kidney Disease in Children (CKiD)

SECTION A: GENERAL INFORMATION

A1. PARTICIPANT ID: AFFIX ID LABEL OR ENTER NUMBER IF ID LABEL IS NOT AVAILABLE

|_|-|_|_|-|_|_|_|

A2. Protocol type: Regular Study Visit..... 0
 Post-Dialysis Visit..... 1
 Post-Transplant Visit..... 2

A3. CKiD VISIT #:

0 2 / 0 1 / 1 8

A4. FORM VERSION:

A5. DATE OF VISIT:

 / /
 M M D D Y Y Y Y

A6. Technologist Initials:

A7. Is this the first CKiD cardiac MRI for the participant? Yes..... 1
 No..... 2

A8. Weight measurement . (kg)

A9. Height measurement . (cm)

SECTION B: MRI STUDY DETAILS

B1. Field Strength: _____

B2. Local Scanner Designation: _____

B3. Coil Used (i.e., 32 channel): _____

B4. What is your software release? _____

B5. Type of Scanner: Philips..... 1 GE..... 3
 Siemens..... 2 Toshiba..... 4

B6. Problems with imaging: ECG gating failure..... 1 Dental braces..... 5
 Poor imaging quality..... 2 Unknown artifacts..... 6
 Pulse sequence conflict..... 3 Other..... 7
 Unexpected system crash... 4 i. Please specify:

SECTION C: DATA

C1. Heart Rate at the beginning of the CMR protocol: (beats per minute)

SECTION D: PATIENT PREPARTION

1. _____ MRI safety screening completed
2. _____ Patient used restroom prior to scan
3. _____ Teaching about breath- holding done
4. _____ Connectors for Cardiac coil and ECG in place
5. _____ ECG electrodes attached according to your MRI manufacturer suggestion

SECTION E: CMR PROTOCOL

1. _____ Subject ID and Site number entered correctly on CD/disc
(no patient name is to be listed on disc or worksheet)
2. _____ MRI CKiD study Completed
 - a. _____ **Multi-Planar Scout**
 - b. _____ Axial SSFP of the chest
 - c. _____ Cine imaging
 1. _____ Pseudo vertical long axis
 2. _____ Short axis scout
 3. _____ 4-chamber cine
 4. _____ 2-chamber cine
 5. _____ Short axis cine stack
 6. _____ Three-chamber cine
3. _____ Tagged imaging
4. _____ Phase contrast velocity imaging
5. _____ T1 mapping
6. _____ "Alert" protocol followed (if applicable) "Alert" Finding (specify) _____
7. _____ CD/Disc copied and stored.

Shipment Directions for CKiD Technologist:

Make a copy of this form. File the copy in the CKiD folder.

Mail original form with anonymized DICOM data:

- **Attn: Michael Taylor, MD, PhD**
CKiD MRI Data
CCHMC
The Heart Institute, ML 2003
3333 Burnet Avenue
Cincinnati, OH 45229
513-803-0426

- **FedEx slip:**
Contact your CCC for a FedEx slip (if needed) and it will be emailed to you

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 33: VASCULAR TESTS: Pulse Wave Analysis, Pulse Wave Velocity, & Heart Rate Variability

33.1 INTRODUCTION

This section discusses the procedures for obtaining the following vascular tests: pulse wave analysis (PWA), pulse wave velocity (PWV), and heart rate variability (HRV). Pulse wave velocity (PWV) and pulse wave analysis (PWA) are measures of arterial stiffness that have been shown to identify individuals at high risk for cardiovascular disease events, such as heart attack and stroke, in several patient populations. There have been several studies using PWV or PWA in subjects with kidney disease but most have been in the dialysis population. Heart rate variability (HRV) is a measure of overall cardiac health and the state of the autonomic nervous system responsible for regulating cardiac activity.

PWV is rather simple to measure conceptually. The CKiD study is interested in a velocity, or speed, of the pressure pulse made by the heart as it circulates through the blood vessels. PWV, like any speed measurement, is calculated by dividing the distance something travels by the time it takes to travel the specified distance. In this case, we measure the distance between the carotid pulse in the neck and femoral pulse in the leg and divide it by the time it takes for the pulse wave to travel the distance between these two sites. Higher PWV measurements are associated with stiffer blood vessels.

PWA is slightly more complex. This measurement takes a tracing of the radial pulse in the wrist and converts it into what that pulse would look like in the aorta, shortly after leaving the heart. From the shape of this aortic tracing we can measure the augmentation index (Aix), another measure of arterial stiffness. Higher Aix values are associated with stiffer blood vessels.

HRV analysis is based on measuring the variability in intervals between R waves (RR intervals). HRV assesses sympathetic and parasympathetic autonomic function by providing stable and evoked measures of HRV. A three-lead ECG non-invasively records a patient's continuous ECG waveforms. From these measurements, parameters (spectral and temporal) related to autonomic nervous system function are calculated.

All three vascular tests (PWA, PWV, and HRV) are measured using the SphygmoCor system (AtCor Medical, Sydney, Australia). Sites with the earlier SphygmoCor model MM3 (powered through wall outlet) will only collect PWA and PWV (not HRV). Sites with the current SphygmoCor model EM3 (powered through computer) and full capabilities will collect PWA, PWV, and HRV. Instructions for how to obtain these measurements in CKiD are detailed below. Additional instructions, including troubleshooting techniques and advice on meeting basic quality control parameters, are provided in the SphygmoCor training manual (Appendix 33. a "SphygmoCor Training Manual") and CKiD-specific training slides developed by Cincinnati Children's Hospital Heart Institute (Appendix 33.b "CKiD Vascular Tests Training Slides"). Both documents can be downloaded from the MOP Section of the CKiD website. The screenshots that follow are from software version 9; if your site has an earlier version, your computer screen may look different, but the content will be the same. A one-page "cheat sheet" is found at the end of this document.

PWA and PWV measurements will each be collected three times per visit. HRV will only be measured once per visit. Thirty minutes total should be allotted to collect PWA and PWV, and an additional 12

minutes should be allotted to collect HRV, if applicable. If more than 15 minutes were dedicated to obtaining PWA measurement(s), move on to the PWV measurement.

The vascular tests will be collected in conjunction with the other cardiovascular measurements at Visit 2 and every other year thereafter (V2, V4, V6, V8...).

33.2 MATERIALS NEEDED

To perform the vascular tests in CKiD, the following items are needed:

- Computer with SphygmoCor software
- SphygmoCor Console
- ECG cords with electrodes
- Foot pedal (optional)
- Alcohol swabs
- Measuring tape
- Dry erase marker

33.3 PROCEDURE FOR COLLECTING VASCULAR TESTS IN CKiD

33.3.1 Hardware setup

Connect the pulse wave velocity (PWV) console to the computer via the serial or USB cable. Connect the power cord to the computer. Connect the power cord to the PWV console. Attach the foot pedal to the rear of the PWV console, if desired, to capture data.

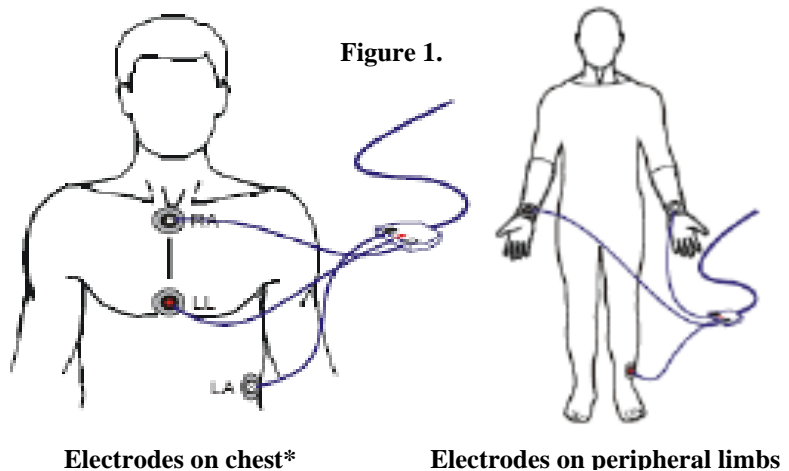
Boot up the computer completely.
Turn the PWV console on by flipping the power switch on the back of the console.

33.3.2 Patient positioning

Instruct the patient to lie supine without any pillows. Attach the ECG lead cord to the front of the PWV console. Use alcohol swabs to remove skin oils and attach the ECG electrodes to the patient's chest.

Attach the white lead (RA) on the top of the sternum, the black lead (LA) on the left side of the

abdomen, and the red lead (LL) on the bottom of the sternum (Figure 1). The QRS complex of the ECG will be positive. If ECG placement on the chest is not possible, use the alternate placement on peripheral limbs (white lead on right arm, black lead on left arm, red lead on left leg).

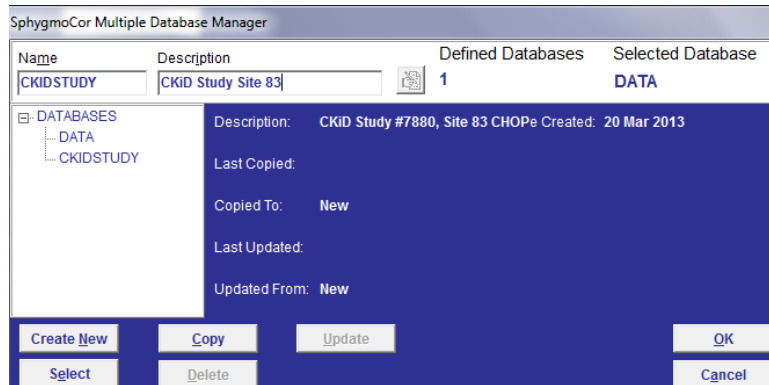


33.3.3 Software setup

Run the SphygmoCor program on the computer. **Open up the “CKIDSTUDY” database.** To open the CKIDSTUDY database, select “System” from the top row of buttons, select “Database manager”, select “CKIDSTUDY” from the list of databases, press the “Select” button, then select “OK” (Figure 2). The CKIDSTUDY database is now the active database; new studies will be stored here and previous CKiD studies will be listed on the left hand side of the screen. *(Note: Studies cannot be transferred between databases; ensure you have the correct database selected. If the CKIDSTUDY database is not listed,*

contact Jon Savant [page 13]; the CKIDSTUDY database should have been created during the initial certification process, see section 33.11 below).

Figure 2.



If the patient has previously had a set of CKiD vascular tests, select the participant by their KID ID on the left hand side of the screen, and continue on to section 33.4 below. If this is the participant’s first set of vascular tests, create a new patient per the following instructions:

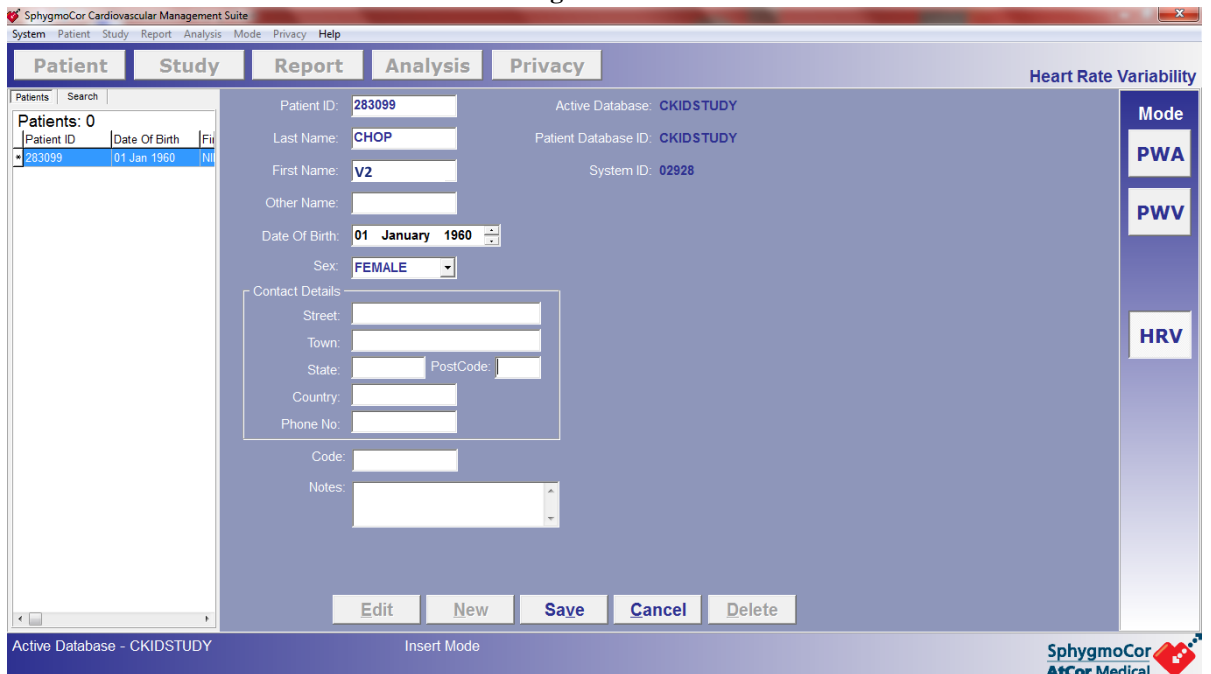
Select the “patient” button on the upper row of buttons.

Select the “New” button from the row of buttons. Confirm a new patient input by clicking “Yes”.

Enter the patient ID information as follows:

- Patient ID: Enter the patient’s CKiD ID number without hyphens (example: enter “283099” for subject 2-83-099).
- Last Name: Enter site initials (example: enter “CHOP” for Children’s Hospital of Philadelphia).
- First Name: Enter Visit number (example: “V2” for Visit 2 (baseline cardiovascular visit); “V4” for Visit 4 (1st follow-up cardiovascular visit).
- Date of Birth: Leave month and day of birth as January 1st, but **change year to 1960** (important for PWA calculation).
- Sex: Select patient’s sex.

Figure 3.



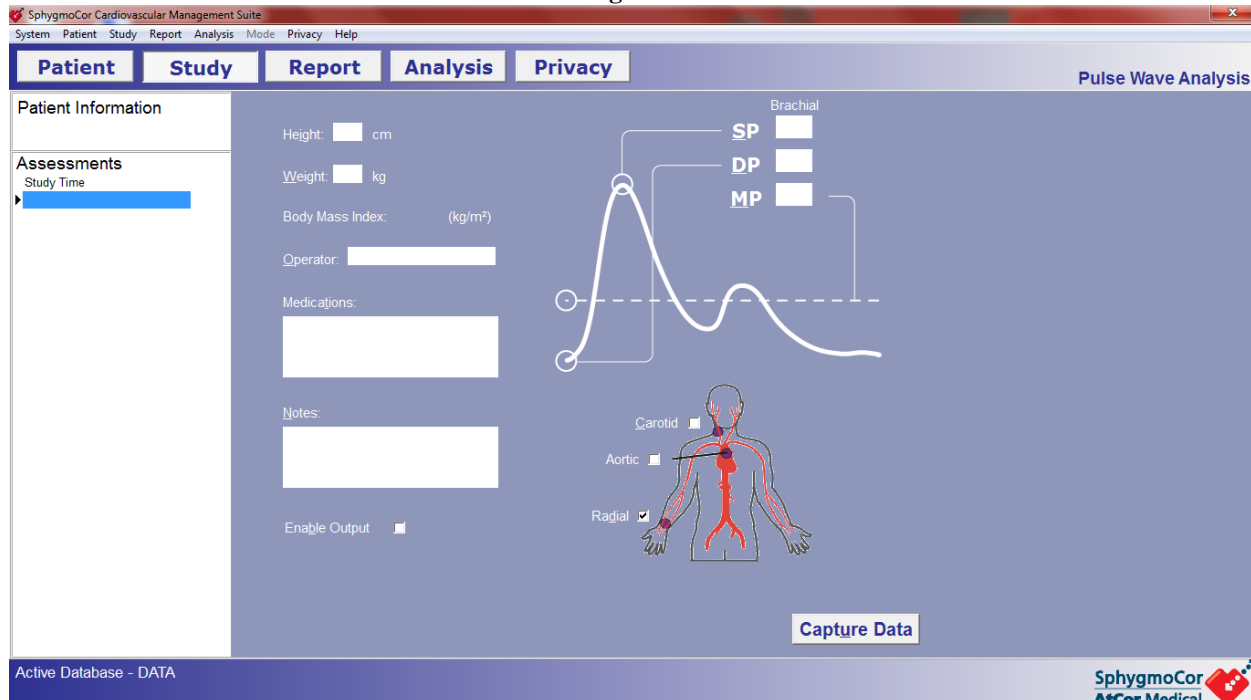
Leave other fields blank.

Click “Save” and then click “Yes” when asked if you want to accept the changes.

33.4 MEASURING AUGMENTATION INDEX (AI) WITH PULSE WAVE ANALYSIS (PWA)

On the “Patient” screen, with the correct participant selected, select the “PWA” button under “Mode” on the right side of the screen. Click the “Study” button from the top row of buttons.

Figure 4.



Enter the values for systolic and diastolic blood pressure in the appropriate dialog boxes using the 2nd of the 3 Mabis blood pressure measurements taken earlier. (*Note: Mabis blood pressure measurements need to be within 6 hours of PWA. If more than 6 hours have elapsed, the mabis blood pressure measurements need to be redone prior to measuring PWA. Automatic/ Dynamap measurements will not suffice.*) The participant should be in the same position during the PWA as s/he was during the BP measurements (i.e., sitting).

For “Operator” enter the technician’s initials.

In the Notes section: Enter the Visit Number (i.e., V2) and whether it is an initial or follow-up PWA. Enter any other general comments.

Leave the height, weight, and medication boxes blank.

Ensure the checkbox for “radial” artery is selected.

Make sure that the “Enable Output” box is not checked.

Select the “capture data” button on the upper right corner of the screen.

33.4.1 PWA Radial Tonometry

Palpate the right radial pulse and place the tonometer directly above the patient's radial pulse, perpendicular to the patient's skin using light pressure (Figure 5). Be sure to remove the plastic cover from the tonometer tip.

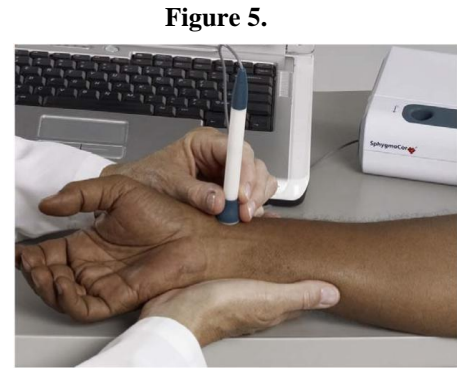


Figure 5.

Assess whether the software is capturing the patient's radial pulse tracing by watching the computer monitor. When approximately 10 seconds of data have been recorded on the computer screen that represents a plausible radial pulse tracing (i.e., waveform), the software will auto-capture the data (alternatively, the operator can step on the foot pedal or press the space bar on the computer to force data capture). The software will switch to a results display screen and the composite tracings, data values, and actual tracings will be visible on the screen. A good quality study will have **all green** and white numbers in the "quality control/QC" column (See Figure 6).

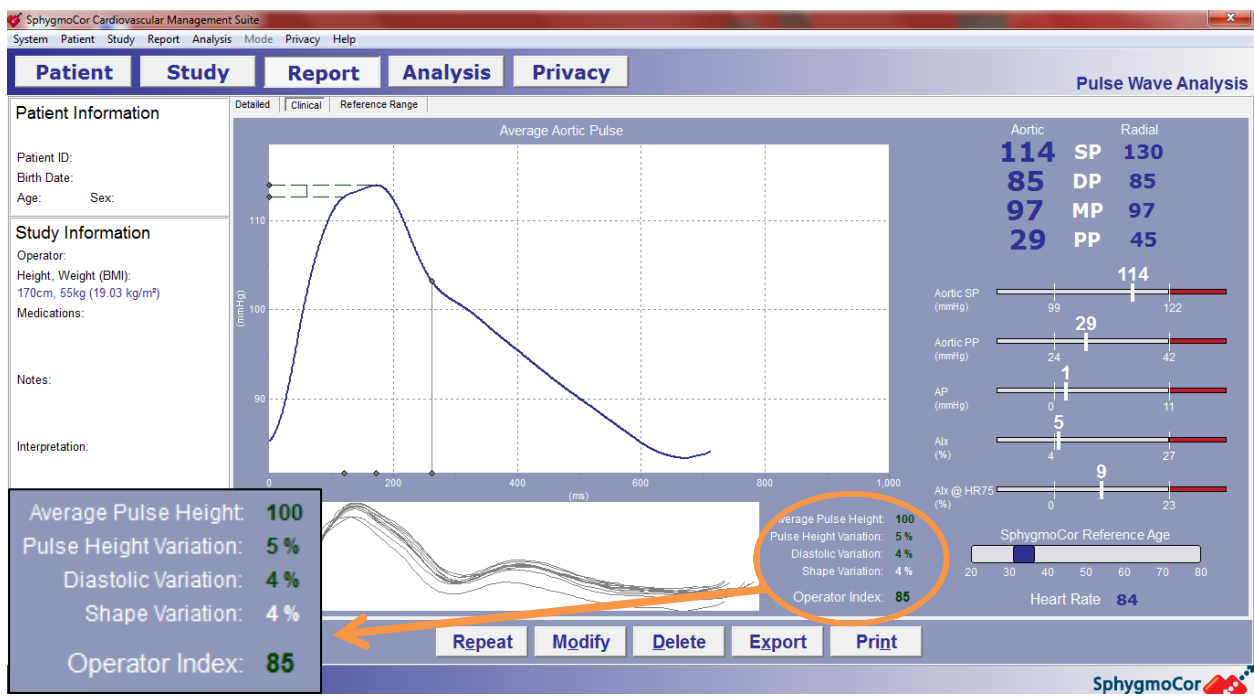
If it is taking a long time to obtain a good quality pulse tracing (i.e., waveform), and the auto-capture feature does not engage, the operator can force data capture when a reasonable waveform has been obtained. Repeat the data collection steps until at least three of the four numbers in the "quality control" column to the right of the tracing are green or white (i.e., one QC number in red will be acceptable).

If a study is clearly non-physiologic or does not meet our quality requirements, please delete the study by clicking on the "delete" button on the lower part of the screen after highlighting the offending study in the left column.

33.4.2 Repeat PWA study

Press the "Repeat" button, and conduct the procedure for obtaining PWA a second time and third time for the same patient. Follow the procedures outlined above in section 33.4.1 (PWA Radial Tonometry). If you are unable to collect a 2nd or 3rd PWA (e.g., due to time constraints), document the reason on the "Protocol Deviation Log.doc" (Section 33.15) and move on to the collection of PWV (Section 33.5).

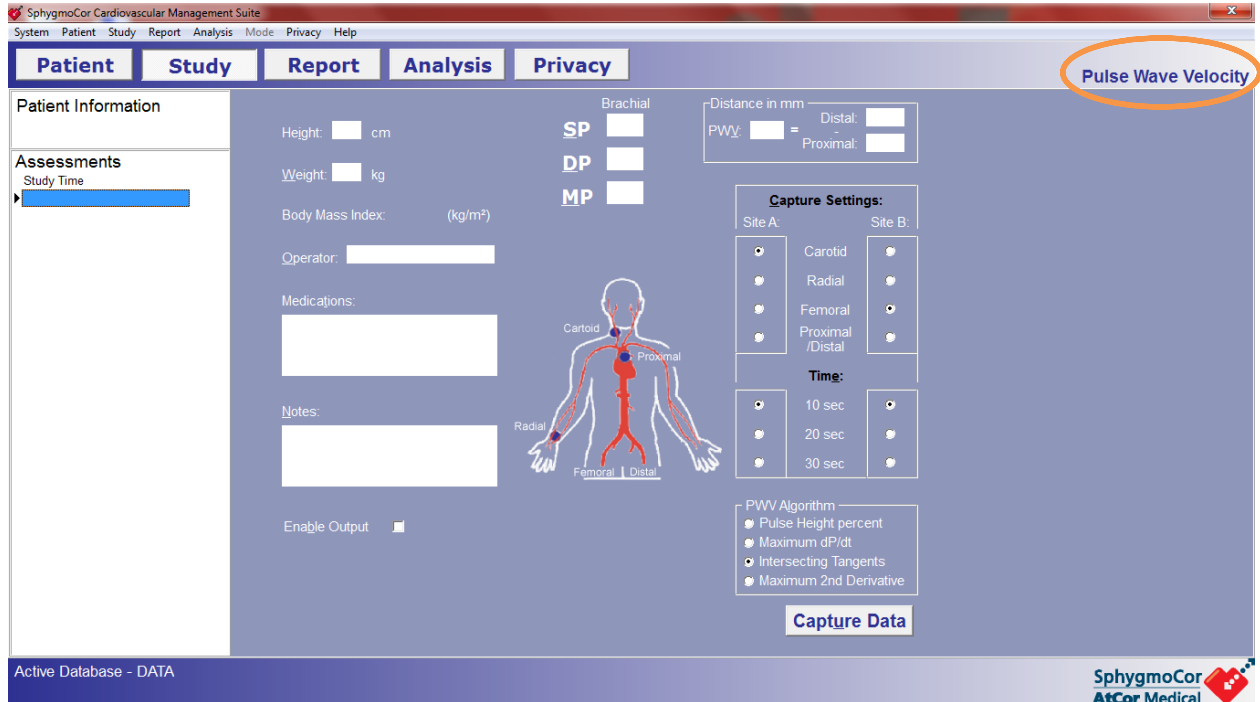
Figure 6.



33.5 MEASURING PULSE WAVE VELOCITY (PWV)

Return to the “Patient” screen, and select the “PWV” button under “Mode” on the right side of the screen. Click the “Study” button from the top row of buttons.

Figure 7.



Ensure the checkbox for “Carotid” is selected under “Capture Settings” for “Site A”.

Ensure the checkbox for “Femoral” is selected for “Site B”.

Enter the values for systolic and diastolic blood pressure in the appropriate dialog boxes using the 2nd of the 3 Mabis blood pressure measurements taken earlier. (*Note: Mabis blood pressure measurements need to be within 6 hours of PWV. If more than 6 hours have elapsed, the mabis blood pressure measurements need to be redone prior to measuring PWV. Automatic/ Dynamap measurements will not suffice*)

For “Operator” enter the technician’s initials.

In the Notes section: Enter the Visit Number (i.e., V2) and whether it is an initial or follow-up PWV. Enter any other general comments.

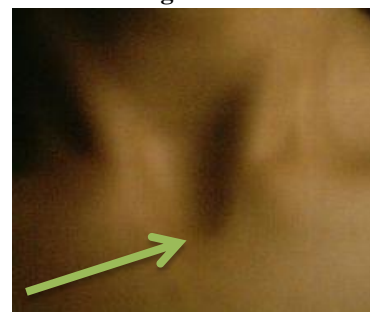
Under “PWV algorithm,” click the circle labeled “Intersecting Tangents” if not already selected. If you do not change this choice, it is the default PWV Algorithm.

Leave “Height” and “Weight” blank.

33.5.1 Measuring Proximal & Distal Distances

Have the participant lie on his/her back. Palpate the right carotid pulse and mark it with the dry erase marker. Using a measuring tape, measure the distance (to the nearest millimeter) from the right carotid pulse to the midline point of the suprasternal notch. The suprasternal

Figure 8.



notch is found at the superior border of the manubrium of the sternum, between the clavicular notches (See Figure 8, arrow).

Repeat the measurement a second time. If these two measures differ by more than 1 centimeter, collect a third measurement. Record the average of these values as the “**proximal**” distance on the PWV page in the SphygmoCor software (Figure 9). Convert measurements in centimeters to millimeters (1 cm = 10 mm). An excel template file (“SphygmoCor Worksheet CKiD.xls”) has been created to assist with these calculations (i.e., average distance, conversion to millimeters) (see Section 33.14). Open the excel template, save it with the KID ID number and visit number in the title, and enter in your measured proximal and distal distances. Press “ALT+TAB” on your keyboard to toggle between excel and SphygmoCor programs.

Palpate the right femoral pulse and mark it with the dry erase marker. Using a measuring tape, measure the distance to the nearest millimeter from the femoral pulse directly to the midline point of the suprasternal notch two different times. If these two measures differ by more than 1 centimeter, collect a third measurement. Record the average of these values as the “**distal**” distance in the SphygmoCor software (Figure 9). Convert measurements in centimeters to millimeters (1 cm = 10 mm). (*Note: do not make adjustments for waist circumference; this will be done during analyses*)

During both measurements, the measuring tape should be directly against the skin (under any clothing) throughout the distance being measured.

Select the “capture data” button at the bottom of the screen. An ECG tracing should be scrolling across the computer monitor with a net positive QRS complex.

Figure 9.

Distance in mm			
PWV:	<input type="text"/>	=	Distal: <input type="text"/>
			Proximal: <input type="text"/>

33.5.2 PWV Carotid Tonometry

Palpate the patient’s right carotid pulse and place the tonometer directly above the patient’s carotid pulse, perpendicular to the patient’s skin, using light pressure (Figure 10). It may help to have the patient turn their head to the left slightly and extend their neck (pick their chin up) to make the carotid pulse more accessible. If where the wave form is captured is greater than 1 cm from where the dry erase mark was made, recalculate the average proximal and distal distances, as described above.



Assess whether the software is capturing the patient’s carotid pulse tracing. When approximately 10 seconds of data have been recorded on the computer screen that represents a plausible carotid pulse tracing timed with the ECG, the software will auto-capture the data (alternatively, the operator can step on the foot pedal or press the spacebar key on the computer to force data capture).

While collecting data, the red tracing represents the patient’s real time ECG and the yellow line represents the pressure values from the tonometer. If the pressure tracing is off the top of the screen when the scale on the left of the screen shows 4000, less pressure should be applied to the tonometer. Similarly, if the pressure tracing is a flat line at the bottom of the computer display below 200, more pressure should be applied to the tonometer.

A message box from the software will pop-up that alerts the technician that the software has correctly captured a tracing from the carotid pulse which the software will call “Site A”. Press enter to begin capturing femoral pulse information.

33.5.3 PWV Femoral Tonometry

Palpate the patient’s right femoral pulse (Figure 11) and place the tonometer directly above the patient’s femoral pulse, perpendicular to the patient’s skin, using light pressure. If where the wave form is captured is greater than 1 cm from where the dry erase mark was made, recalculate the average distances, as described above.

Assess whether the software is capturing the patient’s femoral pulse tracing. When approximately 10 seconds of data have been recorded on the computer screen that represents a plausible femoral pulse tracing timed with the ECG, the software will auto-capture the data (or, the operator can step on the foot pedal or press the space bar on the computer to force data capture).

Figure 11.



The PWV will be calculated and displayed on the bottom of the screen on the results page (Figure 12). Ensure that the following Quality Control (QC) parameters (circled in Figure 12 below) are met:

- The standard deviation (SD) for “ECG-CAR” should be $\leq 6\%$ of the mean time and should be green (not red).
- The SD for “ECG-FEM” should be $\leq 6\%$ of the mean time and should be green (not red)
- The “CAR-FEM PTT SD” should be $\leq 10\%$ and should be green (not red).

If any of the above QC parameters are not satisfied, re-measure the patient’s proximal and distal distances and re-record the carotid and femoral tracings. *(Note: If the above QC parameters are not able to be satisfied, use the following “relaxed” QC parameters: ECG-CAR and ECG-FEM $\leq 10\%$; CAR-FEM PTT SD $\leq 15\%$. If “relaxed” QC parameters are not able to be satisfied, delete the study by clicking on the delete button after highlighting the offending study in the left column.)*

33.5.4 Repeat PWV study

Press the “Repeat” button and conduct the procedure for obtaining PWV a second and third time (only the carotid and femoral tonometry needs to be repeated, not the distance measurements). Follow the procedures outlined above in sections 33.5.2 (PWV Carotid Tonometry) and 33.5.3 (PWV Femoral Tonometry).

If you are unable to collect a 2nd or 3rd PWV (e.g., due to time constraints), document the reason on the “Protocol Deviation Log.doc” (Section 33.15) and move on to the collection of HRV (Section 33.6), leaving the ECG leads on (see Figure 1 on page 2). If not measuring HRV, skip to section 33.7.

Figure 12.



SD/ Mean Time must be ≤6% and appear in green

Site A-B	MeanT(ms)	SD(ms)	N	HR(bpm)
ECG-CAR	129.1	3.2	6	56
ECG-FEM	205.4	4.1	8	56
CAR-FEM	76.3	5.2		

CAR-FEM PTT SD 6.9 %
 Pulse Wave Velocity (m/s) 4.6 ± 0.3

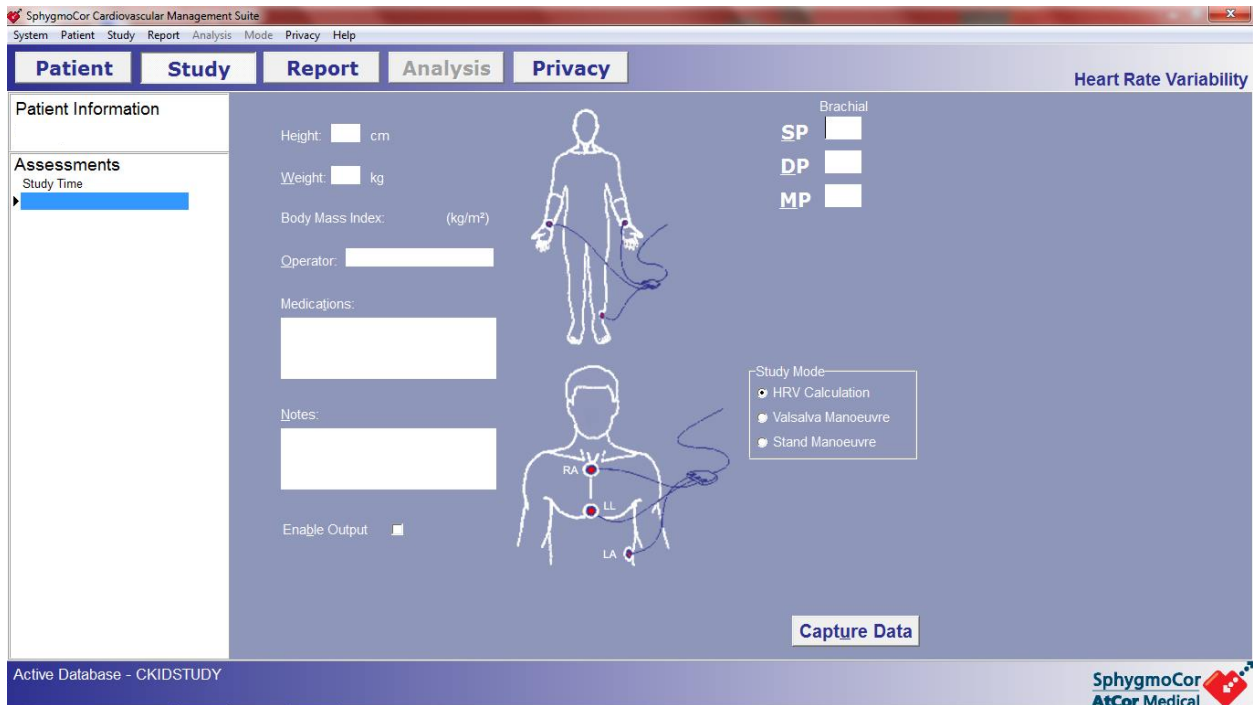
CAR-FEM PTT SD must be ≤10% and appear in green

33.6 MEASURING HEART RATE VARIABILITY (HRV)

Note: HRV can only be measured using SphygmoCor model EM3, software version 9 or greater, with HRV capabilities (CVPH). The model is listed on the back of the device (EM3 model does NOT plug into wall outlet); the software version and capabilities are found by clicking “Help” then “About” from the toolbar. If HRV is not an option, your device does not have HRV capabilities.

Return to the “Patient” screen, select the “HRV” button under “Mode” on the right side of the screen. Click the “Study” button from the top row of buttons.

Figure 13.



Enter the values for systolic and diastolic blood pressure in the appropriate dialog boxes using the 2nd of the 3 Mabis blood pressure measurements taken earlier. (*Note: Mabis blood pressure measurements need to be within 6 hours of HRV. If more than 6 hours have elapsed, the mabis blood pressure measurements need to be redone prior to measuring HRV. Automatic/ Dynamap measurements will not suffice.*)

For “Operator” enter the technician’s initials.

In the Notes section: Enter the Visit Number (i.e., V2) and whether it is an initial or follow-up HRV. Enter any other general comments.

Leave the height, weight, and medication boxes blank.

Ensure that ECG leads are on per instructions in Figure 1 on page 2.

Inform the participant that the test is about to begin, and that they will need to lay as still as possible for the next 10 minutes, without holding their breath or falling asleep.

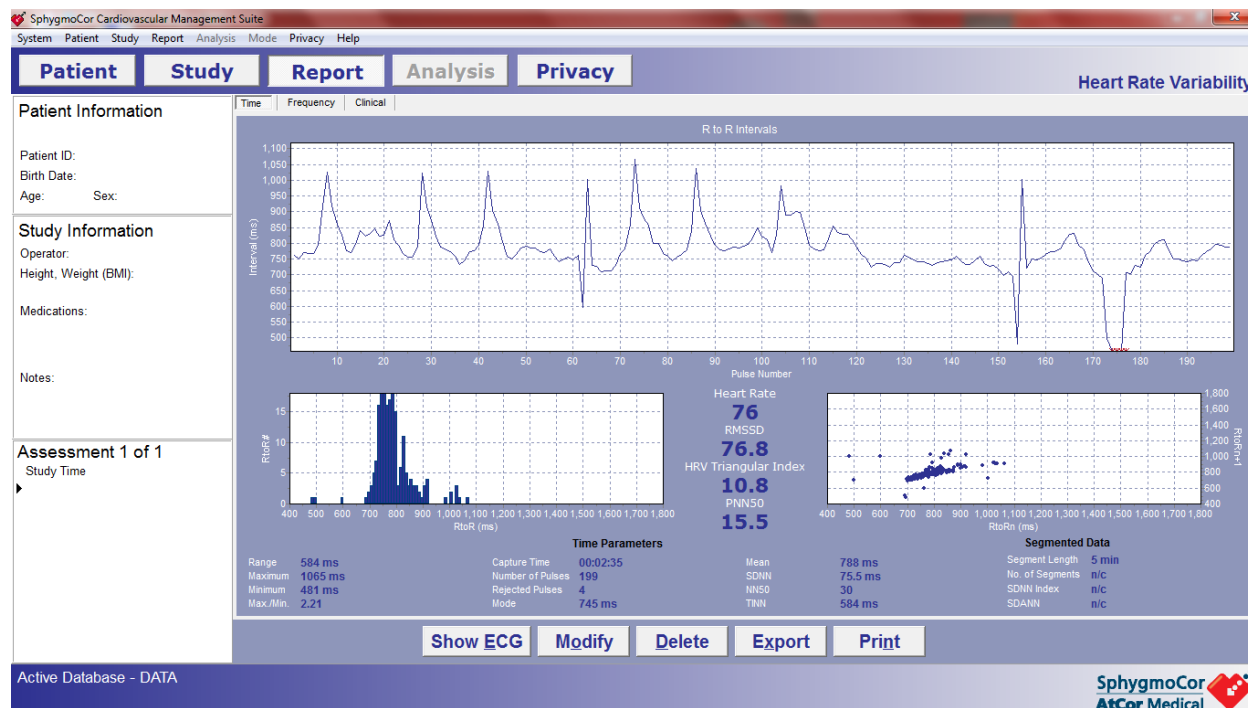
Press the “Capture button”.

During the capture, the blue ECG indicator labeled on the front panel will be illuminated. A horizontal trace of ECG will appear in the ECG Data Capture Window. If the ECG trace is poor (i.e., irregular baseline or T-waves that are as tall as the QRS), re-prep the skin or use abrasive ECG prep paste; if still poor, change the ECG leads (leads can dry out).

When satisfied with the quality of the signals, start recording by pressing the “Start Session” button on the top right of the screen. The beat-to-beat R-to-R intervals chart will now be activated and updated every 5 seconds.

After 10 minutes of good quality data, press the “Calculate” button in the top right of the capture screen or press the footswitch. The HRV Report Screen will be displayed (Figure 14). Examine the report for quality: The plot shows beat to beat R-to-R intervals of the whole recording. An interval marked with a red star indicates that it had been rejected and it will not be used in the HRV calculation. An interval will be rejected when it is uncharacteristically too high or too low compared to previous intervals. Ectopic beats are automatically discarded from the ECG. Ectopic beats are defined as significant changes to the R-to-R intervals from the previous beat. As long as the number of ectopic beats is <35% of the total number of beats, the HRV calculation will be deemed acceptable.

Figure 14.



On the “Report” tab, look for inconclusive labels at the bottom of the screen below the action buttons. **If there are any inconclusive labels, the study should be discarded and the measurement repeated.** An “Inconclusive” label will appear if one of the following parameters is too large:

1. Percentage of rejected pulses (pulses with very high or very low R-to-R values) compared to accepted pulses
2. RMSSD (Root mean squared successive difference of NN intervals)
3. PNN50 (Proportion of successive R-to-R intervals with a difference greater than 50ms)

33.7 POST MEASUREMENT

Prior to saving the individual study, ensure that **no private health information is included** (see Figure 3 on page 3 above for a description of how to record the patient ID information).

Turn off the SphygmoCor device by flipping the power switch on the back of the device.

Quit the SphygmoCor software package on the computer. **Be sure to exit the SphygmoCor program before disconnecting the USB cable from the computer.** If you disconnect the SphygmoCor device from the computer prior to exiting the software, **the computer may crash.**

Once the software has closed, disconnect the device from the computer. Disconnect the foot pedal if you are using it.

Data should be backed up on a separate computer by re-saving the SCOR.mdb database where all the data is saved.

33.8 EXPORTING DATA

The “CKIDSTUDY” database containing all PWA, PWV, and HRV measurements for CKiD will be exported as a .txt file and sent to CKIDPWV@email.chop.edu on a monthly basis (or after each new set of measurements, whichever is less frequent). SphygmoCor can export data in two formats (text [.txt] or graphic [.jpg]) and can export all data in a database, all data for one patient, or one report for one patient. For CKiD, **export the entire CKIDSTUDY database as a text file** each time.

To export the CKIDSTUDY database as a .txt file, navigate to the patient screen by clicking on the ‘patient tab’ from the top row of buttons. From the tool bar, select ‘System’ → ‘Database’ → ‘Export’. Select ‘Export All Measurements in the Database’ (*Note: ensure that the CKIDSTUDY database is the active database; see section 33.3.3 on page 2 for more information*). This will allow all readings for one type of measurement from all CKiD participants in the CKIDSTUDY database to be exported. The process will need to be repeated for exporting all PWV, PWA, and HRV studies. After clicking ‘Export’, the SphygmoCor export window will appear with a default file name and default file location to which the file will be exported; there is no need to change the file name. The default file name is prefixed with ‘All’ and is followed by the database name and the date of exporting and the mode the readings were taken in; eg:

For PWA: C:\Program Files\SphygmoCor\Export\All_CKIDSTUDY_1Dec2012_pwa.txt

For PWV: C:\Program Files\SphygmoCor\Export\All_CKIDSTUDY_1Dec2012_pvw.txt

For HRV: C:\Program Files\SphygmoCor\Export\All_CKIDSTUDY_1Dec2012_hrv.txt

After exporting all studies for each type of measurement (i.e., PWV, PWA, HRV), send the text files by email to CKIDPWV@email.chop.edu. If any new issues were reported on the “Protocol Deviation Log”, this file should also be emailed. If your computer does not have web/email access, you will need to copy the text files to a thumbdrive/external harddrive and transfer them to a computer that does have email capabilities.

If any of the studies were initially recorded in the wrong database (i.e., in a database other than the CKIDSTUDY database), contact Jon Savant (contact info on page 13) for instructions on how to proceed.

33.9 SAMPLE DESCRIPTION OF PWV AND PWA STUDIES TO CKiD PARTICIPANTS

Below is a brief script that can be read to the participant to describe the PWV and PWA tests and procedures.

“The next test will attempt to measure the stiffness of your blood vessels. This test measures what is called ‘pulse wave velocity’ and ‘pulse wave analysis’. We will do this non-invasively by attempting to take pictures of your pulse in three different locations using a pencil-like wand with a pressure-sensing tip on its end. This wand is placed over your skin above the location where a pulse can be felt. By measuring the distance between these pulses and the time that it takes for your pulse to travel between these locations, we can measure the velocity, or speed, of your pulse.

Knowing the speed of your pulse gives us a good indication of how stiff your blood vessels are. Stiffer blood vessels cause the pulse to travel faster through the body.

We are testing whether stiffer blood vessels put a patient at risk for cardiovascular (heart) complications or renal (kidney) complications in the future.

We will also measure the variability of your heart rate. To do this, you will lie still for 10 more minutes and your heart beat will be measured with the electrocardiogram electrode pads attached to your chest.

Important Note: Emphasize to each patient that understanding the significance of these data (PWV and PWA) is the ultimate goal of this research. We will be in a much better position to know what any individual subjects’ values mean (and importantly, in the future, how they may be treated) after several years of observation.

33.10 QUESTIONS

Please direct questions and concerns to the individuals listed below.

Jon Savant, B.S.

Clinical Research Coordinator

The Children's Hospital of Philadelphia

Telephone: 267-426-8386

Email: SavantJ@email.chop.edu, cc: CKIDPWV@email.chop.edu

Jackie Ndirangu, MPH

Project Director, East Coast Clinical Coordinator Center

The Children's Hospital of Philadelphia

Telephone: 267-426-8388

Email: NdiranguJ@email.chop.edu

Susan Furth, M.D., Ph.D.

Chief, Division of Nephrology

The Children's Hospital of Philadelphia

34th Street and Civic Center Boulevard

Philadelphia, PA 19104-4399

Telephone: 215-590-2449

E-mail: FurthS@email.chop.edu

33.11 INITIAL CERTIFICATION

Prior to collecting data for CKiD, operators will need to create a separate database in the SphygmoCor program where the qualification studies will be stored. To create a new database, select “System” from the top row of buttons and select “Database manager”. The Database manager window will appear (see Figure 2 on page 3). Enter in “TRAINING” for “Name”, and “Training for CKiD Study Site XX” for “Description” (where XX is your actual site number). Select “Create New” and select “OK”.

Only those operators that have successfully been qualified by the Vascular Tests Coordinating Center (VTCC) may collect Vascular Test data for CKiD. The following files need to be sent to CKIDPWV@email.chop.edu for operator qualification:

1. Text files containing the data exported from the ‘TRAINING’ database; one containing all 9 PWV studies, one containing all 9 PWA studies, and one containing all 9 HRV studies (see Section 33.8, “Exporting Data”).
2. Completed Excel file: “Vascular Certification Log CKiD.xls”
3. Images of all 9 PWA waveforms must be submitted for visual inspection. You can export the images as .jpeg or .pdf files (choose from one of two options below):
 - a. Export as .jpeg
 - i. On ‘Report’ screen, click on ‘Export’ (Export window will be displayed.)
 - ii. Click on ‘Select’, navigate to where you want to save the file, click ‘Open’
 - iii. Click ‘Export’ and study will be exported as a picture (.jpeg file)
 - b. Export as .pdf
 - i. On ‘Report’ screen, click on ‘Print’
 - ii. Click ‘Yes’ when asked “Would you like to print report”
 - iii. A window will be displayed and you can navigate to where you want to save the file
 - iv. Modify the name of the file and click ‘OK’; the file will be exported as a .pdf file

Note: If your SphygmoCor laptop is not connected to the internet, you will need to transfer the necessary files to a different computer using a thumbdrive.

Initial certification for trained operator:

1. Protocol review
2. Performance of 3 independent PWV, PWA, and HRV measurements on 3 standard subjects or volunteers (not a CKiD subject) (3 measures of 3 tests on 3 subjects = 27 total) (If not doing HRV, 3 measures of 2 tests on 3 subjects = 18 total).
 - a. Files will be sent to CKIDPWV@email.chop.edu for feedback on technique.
 - b. Statistician will calculate coefficients of variability and intraclass correlation coefficients for PWV, PWA, and HRV.
 - i. Coefficients of variability $\leq 10\%$ required to be certified as successfully trained to measure PWV.
 - ii. Intraclass correlation coefficients ≥ 0.7 required to be certified as successfully trained to measure PWA.
 - iii. Intraclass correlation coefficients ≥ 0.5 required to be certified as successfully trained to measure HRV.

Initial training and certification for new operator:

1. Protocol review
2. Attend off-site training session. The course will include didactic lectures (theory of arterial stiffness) and hands-on training.
3. Performance of 3 independent PWV, PWA, and HRV measurements on 3 standard subjects or volunteers (not a CKiD subject) (3 measures of 3 tests on 3 subjects = 27 total) (If not doing HRV, 3 measures of 2 tests on 3 subjects = 18 total).
 - a. Files will be sent to CKIDPWV@email.chop.edu for feedback on technique.
 - b. Statistician will calculate coefficients of variability and intraclass correlation coefficients for PWV, PWA, and HRV.
 - i. Coefficients of variability $\leq 10\%$ required to be certified as successfully trained to measure PWV.
 - ii. Intraclass correlation coefficients ≥ 0.7 required to be certified as successfully trained to measure PWA.
 - iii. Intraclass correlation coefficients ≥ 0.5 required to be certified as successfully trained to measure HRV.

After sending the qualification files to CKIDPWV@email.chop.edu, the operator and/or study coordinator will receive a confirmation email that they have been received. The studies will be reviewed for quality and reproducibility and a detailed letter containing feedback will be emailed to the operator, study coordinator and local site PI. Operators that have been successfully qualified, will also receive a certificate saying as such. After being qualified, a new dataset should be created in SphygmoCor by following these steps: Select “System” from the top row of buttons and select “Database manager”. The Database manager window will appear (see Figure 2 on page 3). Enter in “CKIDSTUDY” for “Name”, and “CKiD Study Site XX” for “Description” (where XX is your actual site number). Select “Create New” and select “OK”.

33.12 QUALITY CONTROL / QUALITY ANALYSIS PLAN

For ongoing quality control purposes, the operator at each site must submit at least one PWV, one PWA, and one HRV study (HRV at participating sites only) at regular intervals for review. Ideally, this should happen every 3 months (but no longer than 6 months). If there are no CKiD participants scheduled during this interval, the operator must submit one PWV, one PWA, and one HRV study on a single standard subject or volunteer (not a CKiD subject).

Adequacy of Individual Studies:

We will assess the adequacy of studies by evaluating quality control indices built into the SphygmoCor software.

In the pulse wave velocity mode, the “CAR-FEM PTT SD” should be $\leq 10\%$. Furthermore, the standard deviation of the component transit times (“ECG-CAR” and “ECG-FEM”) should be $\leq 6\%$ of the time measures for a study to be adequate. In all cases, the QC parameters should be listed in green or white (not in red).

In the pulse wave analysis mode, we will monitor tonometry values such that at least 3 of 4 quality control indices must be green or white (rather than red) for a study to be considered adequate. The four quality control parameters are as follows:

1. Pulse Height ≥ 80
2. Pulse Height Variation ≤ 5
3. Baseline/diastolic Variation ≤ 5
4. Shape Deviation ≤ 4 .

Additionally, the Operator Index should be ≥ 80 . The Operator Index is an amalgam PWA quality control parameter based on the four main parameters above, each assigned a different weight.

In the heart rate variability mode, the number of ectopic beats should be $<35\%$ of the total number of beats. Additionally, there should be no “Inconclusive” labels in the report. An “Inconclusive” label appears when one of the following three parameters is too large:

1. Percentage of rejected pulses (pulses with very high or very low R-to-R values) compared to accepted pulses
2. RMSSD (Root mean squared successive difference of NN intervals)
3. PNN50 (Proportion of successive R-to-R intervals with a difference greater than 50ms)

Operators that submit two consecutive deficient studies must be re-certified on standard subjects as described above in the patient certification section.

33.13 ALERT PROTOCOL

A ‘flag procedure’ is the protocol used to notify the Principal investigator at the local site of an abnormal study. The site PI will determine if the abnormality requires additional evaluation or treatment.

Criteria to flag a study:

- a. Abnormal blood pressure (BP), very high ($>160/100$) or very low ($<80/50$)
- b. Abnormal heart rate (HR)
 - i. Very fast or slow HR (HR > 150 or < 50)
 - ii. Very irregular HR
 - iii. Abnormal beats (arrhythmia) - any very unusual ECG tracing
 - iv. Any study that makes the operator feel “uncomfortable”

Each site will report the ‘flagged’ procedure to their site PI and the Vascular Tests Coordinating Center (VTCC) at email address: CKIDPWV@email.chop.edu or phone number: 267-426-8386. If the abnormality is deemed “Urgent”, the local site PI should be paged immediately. Urgent = Abnormal BP or HR associated with dizziness, shortness of breath, chest pain or other symptoms. If “non-urgent”, download a “screen shot” of the image from the device as per protocol and email with a description of the suspected abnormality to the local site PI and to the VTCC at CKIDPWV@email.chop.edu . The VTCC will also contact the local site PI within 1 to 2 weeks with an interpretation and any additional instructions.

33.14 SPHYGMOCOR WORKSHEET

Below is an example of a blank “SphygmoCor Worksheet CKiD.xls”; the template file should be saved to the laptop. The PWV distance measurements (proximal: carotid → SSN; & distal: SSN → femoral) are entered and the average value and conversion from centimeters to millimeters are automatically calculated. Below the blank worksheet is an example of a completed worksheet. Completed worksheets files may be saved with the KID ID and visit number for future reference.

Subject ID Number:		
Summary		
Proximal Carotid (mm)	#DIV/0!	This will convert CM to MM
Distal Femoral (mm)	#DIV/0!	This will convert CM to MM

CAROTID to SSN (<i>Proximal all</i>)	Value	Total	AVG PROXIMAL
Measure #	cm	all 3 values	Divide Total by 3
#1		0	#DIV/0!
#2			
#3			

SSN to Femoral	Value	Total	AVG SSN to Femoral
Measure #	cm	all 3 values	Divide Total by 3
#1		0	#DIV/0!
#2			
#3			

Subject ID Number: 2-99-999		
Summary		
Proximal Carotid (mm)	100	This will convert CM to MM
Distal Femoral (mm)	500	This will convert CM to MM

CAROTID to SSN (<i>Proximal all</i>)	Value	Total	AVG PROXIMAL
Measure #	cm	all 3 values	Divide Total by 3
#1	9.8	30	10
#2	10.2		
#3	10		

SSN to Femoral	Value	Total	AVG SSN to Femoral
Measure #	cm	all 3 values	Divide Total by 3
#1	49.8	150	50
#2	50.2		
#3	50		

33.15 PROTOCOL DEVIATION LOG

Below is a blank “Protocol Deviation Log”. This should be filled out if there are any anomalies with a particular study, such as running out of time before 3 measures were collected, or any special circumstances that could have compromised the study (e.g., obesity, room temperature, vasoactive drug use, entered automatic or non-sitting blood pressure, etc.). Below the blank log is an example of a completed log.

CKiD Vascular Protocol Deviation Log

ID#	Date	Measure Time	Measure Type	Staff ID (initials)	Protocol Deviation	Needs Physician Review: Y or N

EXAMPLE: CKiD Vascular Protocol Deviation Log

ID#	Date	Measure Time	Measure Type	Staff ID (initials)	Protocol Deviation	Needs Physician Review: Y or N
2-99-996	1/19/2013	8:53; 9:00	PWA	JED	Only got 2 PWA in over 1 hour	N
2-99-997	1/20/2013	10:09	PWV	SRO	Only got 1 PWV due to severe ADHD	N
2-99-990	1/19/2013	10:01:09	HRV	HHM	HRV may have artifact	Y
2-99-992	1/21/2013	10:14	PWV	STR	Only got 1 PWV due to obesity	N

33.16 CKiD Vascular Tests Cheat Sheet (See MOP Sections 33.1-33.15 for full details)

1. Prior to assessment, record the following in the protocol deviation log excel file:
 - a. If recently used vasoactive drugs
 - b. If BP entered was not obtained sitting or was not auscultatory (*Note: use 2nd of 3 Mabis blood pressures collected within last 6 hours*)
 - c. If ambient room temperature is too hot or cold

2. If using Excel worksheet for calculations, save as new name using CKID & visit number (e.g., 283100v2)

3. Synopsis of Guidelines for each test:
 - a. PWA – 3 readings – Perform with subject SITTING (time limit 15 minutes)**
 - i. Average Pulse Height: must be ≥ 80
 - ii. Pulse Height Variation: should be $\leq 5\%$ (max 10%)
 - iii. Diastolic Variation: should be $\leq 5\%$ (max 10%)
 - iv. Shape variation between should be $\leq 4\%$ (max 8%)

 - b. PWV – 3 readings – Perform with subject lying down (time limit 15 minutes)**
 - i. *Measure the Femoral and Proximal (Carotid) Distance-* The RIGHT side is preferred. If Left used, note reason in protocol deviation log
 - ii. Quality Guidelines:
 1. The first two values (ECG-CAR and ECG-FEM) should be in **GREEN** not **RED** (ignore CARFEM). This means SD is $\leq 6\%$ (max 10%)
 2. For Femoral, PTT SD should be **GREEN** (means PWV SD $\leq 10\%$) (max 15%)
 3. Difference in HR between Proximal and Distal should be ≤ 5 BPM (may be hard in younger kids)
 - iii. If your final recording position is >1 cm from your original mark: Re-measure 3 times and enter into spreadsheet to get average

 - c. Heart Rate Variability (select sites only) – Perform with subject lying down**
 - i. Make sure the patient does not talk or move during the test
 - ii. 10 minutes of good quality data (will accept no data <9 or >11 min)
 1. RMS SD (should be < 250)
 2. PNN50 (should be <70)
 3. R wave should be upright

4. Record in protocol deviation log any difficulties with obtaining quality measures

5. Within a month of each visit, export cumulative datasets as text file and send to CKIDPWV@email.chop.edu



SphygmoCor[®] CPV Clinical System Training



Topics

- SphygmoCor® CPV Clinical System Overview
- Pulse Wave Analysis and Wave Reflection
- Pulse Wave Analysis Indices
- SphygmoCor Patient Screen
- Performing Pulse Wave Analysis
- Pulse Wave Velocity
- Software Overview & Reference



SphygmoCor[®] CPV Clinical System Overview

SphygmoCor[®] CPV System

What is the SphygmoCor CPV System?

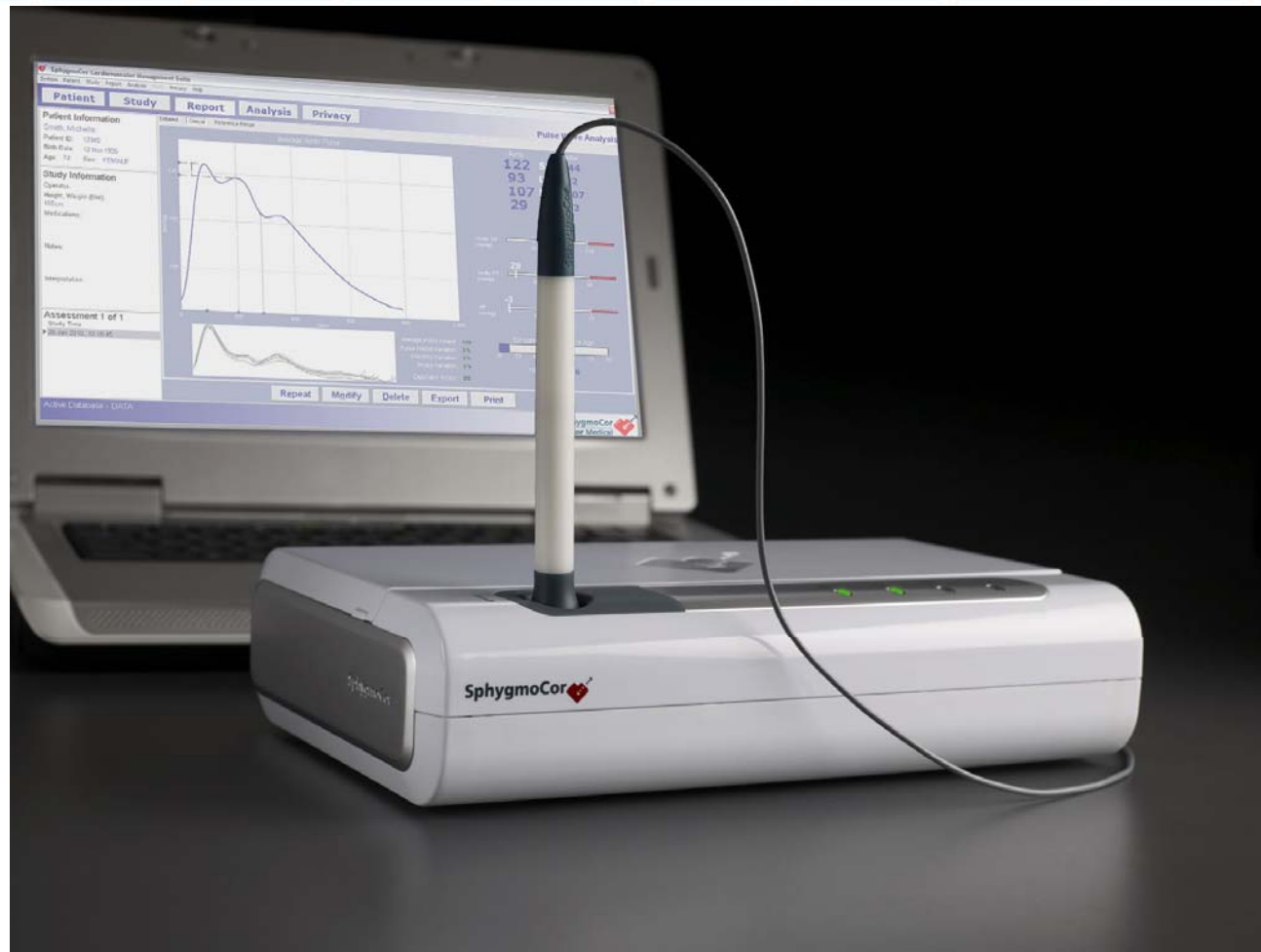
A **non-invasive tool** used for measuring **central arterial pressure** and indices that characterize the central pressure waveform. Assessment of the central pressure waveform provides:

- Individual-specific information regarding **arterial stiffness**
- Effects of the reflected pressure wave on **LV load, myocardial perfusion, and ventricular-vascular coupling**

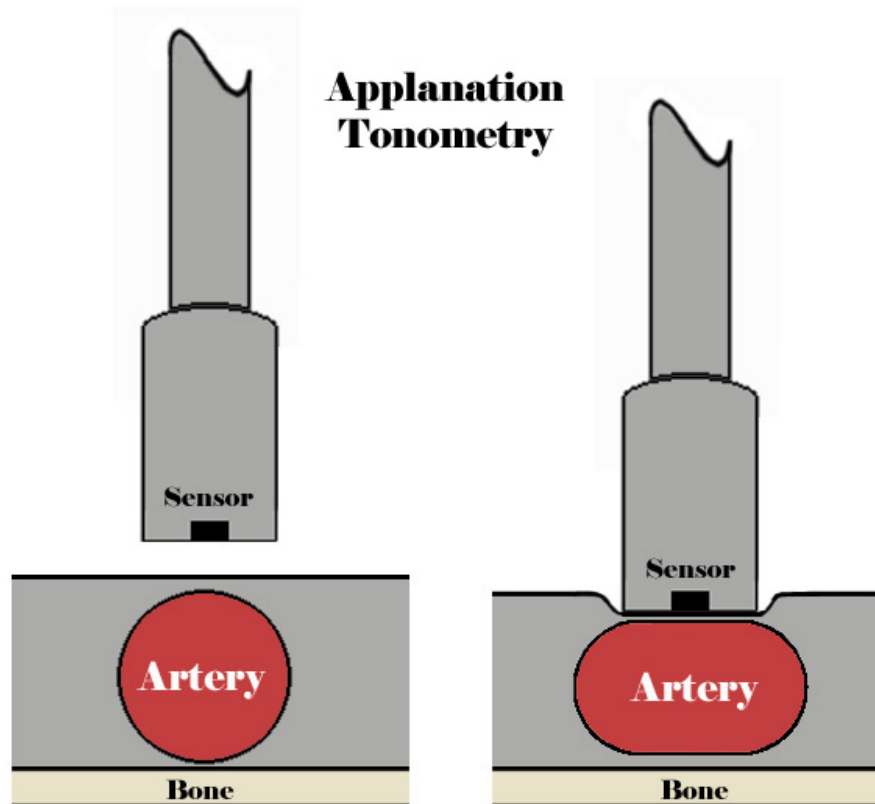
When included in the assessment and management of hypertension patients, the SphygmoCor System provides:

- More precise and individualized assessment of cardiovascular risk than standard blood pressure measurements
- Therapy guidance in difficult-to-treat and borderline hypertensive patients
- Individualized assessment of the effects of anti-hypertensive therapies on the pressure at central organs such as the heart, kidney, and brain

The SphygmoCor® CPV System



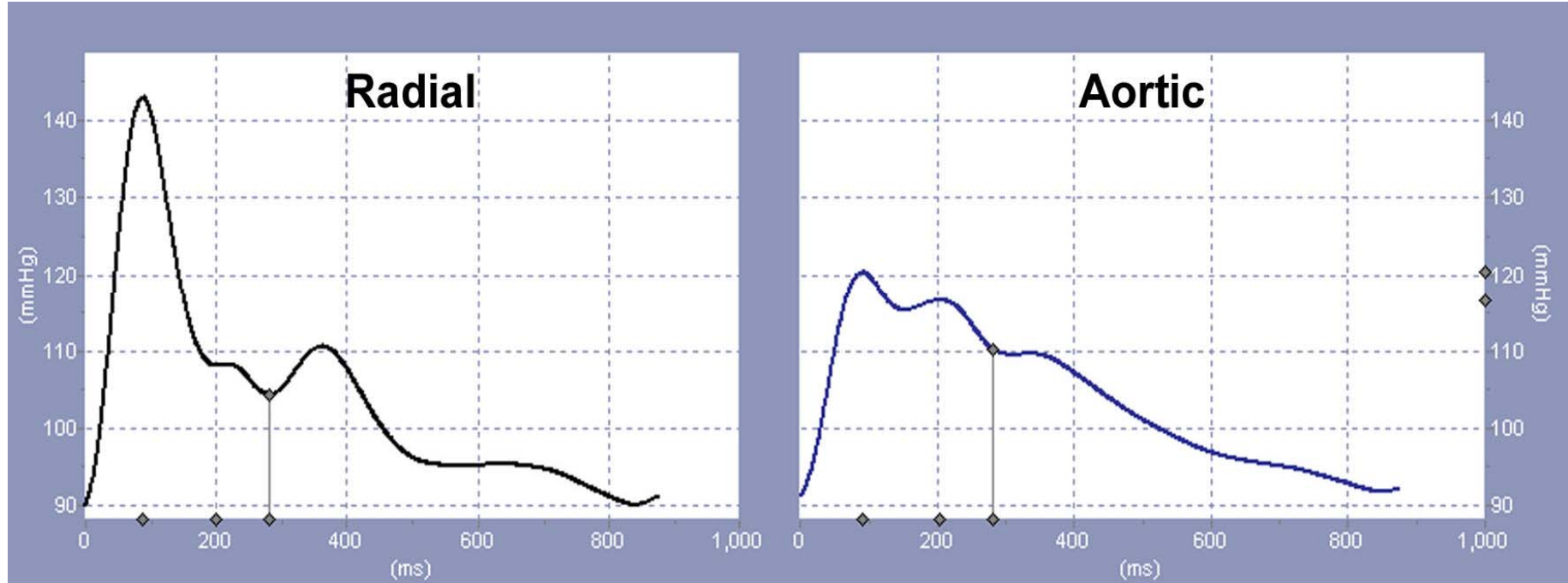
Applanation Tonometry



- Applanation tonometry is used at the radial artery to measure pressure waveforms
- A mathematical transfer function* derives the ascending aortic waveform
- This technique is known as Pulse Wave Analysis (PWA)

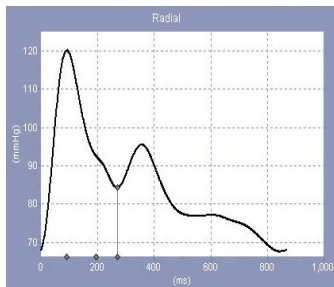
*Generalized transfer function cleared by FDA

Radial and Central Pressure Waveforms

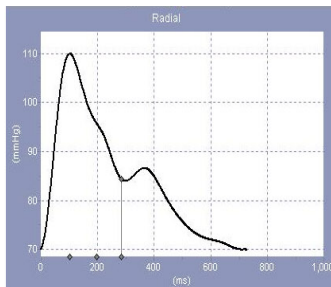


Radial Waveform Shapes

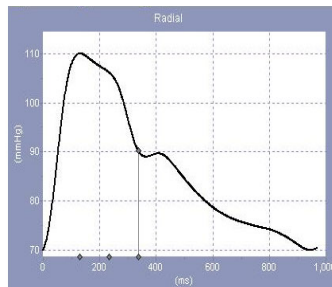
The shape of the radial waveform changes over time due to vascular changes associated with aging. These changes can also result from various disease states.



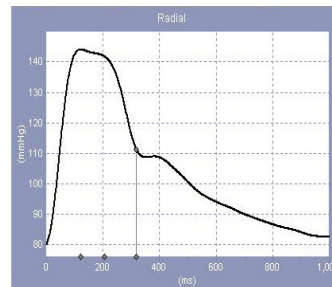
20 year old



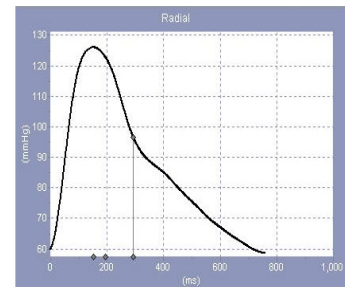
30 year old



40 year old



50 year old



70 year old



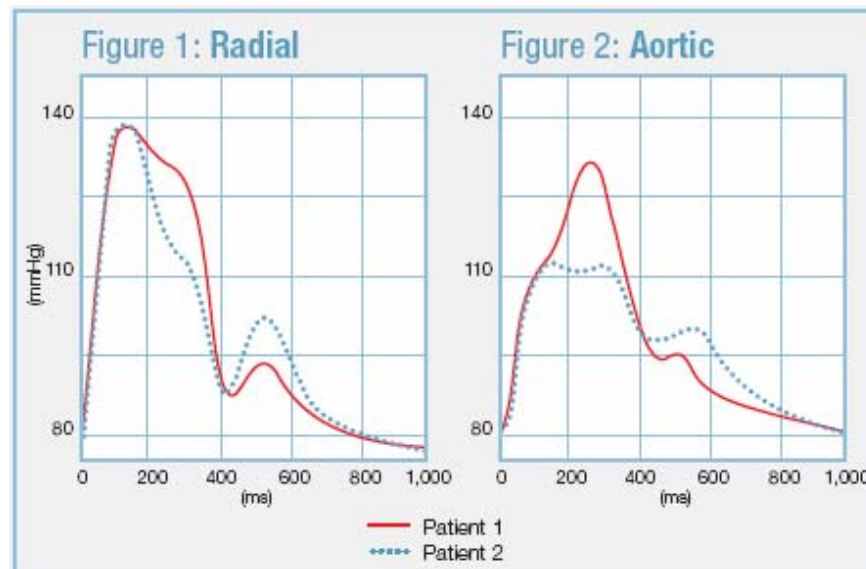
Pulse Wave Analysis and Wave Reflection

Pulse Wave Analysis

- Systolic Pulse Pressure is always lowest at the heart
- Pulse pressure measured in the brachial artery may be up to **20-50% greater** than that in the aorta
 - This amplification depends primarily upon the stiffness of the aorta as well as differences in individual physiology
 - Stiffness can vary with age, gender and cardiovascular disease

Brachial Pressure Differs from Central Pressure

Brachial Cuff BP vs. Central BP



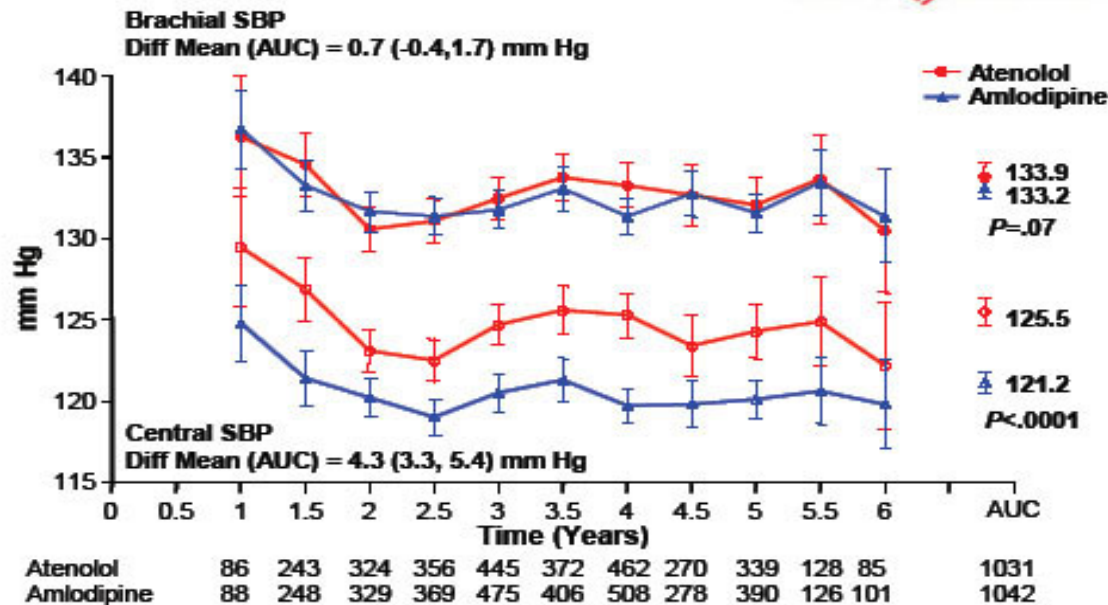
TWO PATIENTS with the same systolic and diastolic brachial/radial pressures (Figure 1), but with very different central/aortic pressures (Figure 2).

- **Brachial cuff BP is NOT adequate for managing central systolic pressure**
- **Why are the two central systolic pressures different?... the patients have different degrees of arterial stiffness**

Effect of Drug Therapy on Central Pressure

Brachial and Central Aortic Systolic Blood Pressure (\pm 95% CI)

ascot
cafe  conduit artery functional evaluation

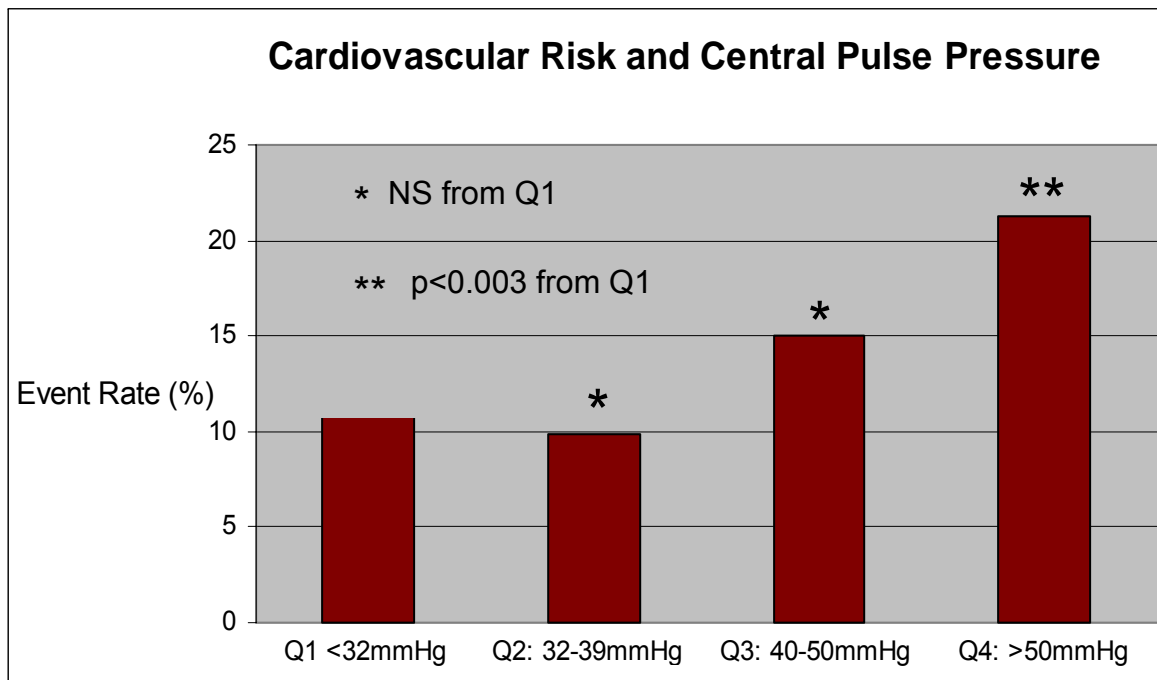


CAFE Study

- > 2,000 patients
- Brachial BP controlled in both study arms
- One study arm had up to 30% > CV events than the other arm
- At the end of the study, patients with a lower central pressure had a greater benefit



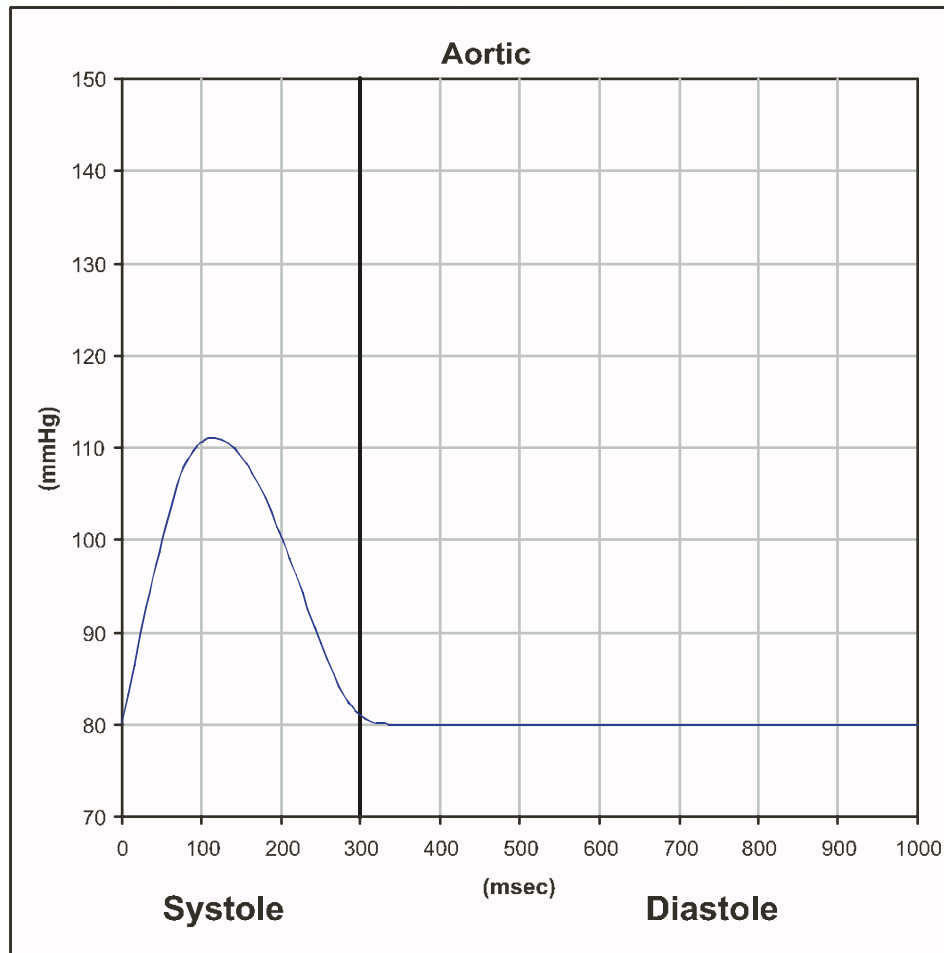
Central Pressure is More Predictive of Outcome than Brachial Pressure



- Multi-year, NIH-funded study in 3,520 high-risk patients

- Demonstrated that central pulse pressure was more strongly predictive of CV events
- Specifically, central pulse pressures ≥ 50 mmHG had a 20% chance of having a CV event in the next 5 years
- Brachial pulse pressure did not show a similar threshold

Pressure Wave Reflection at the Heart

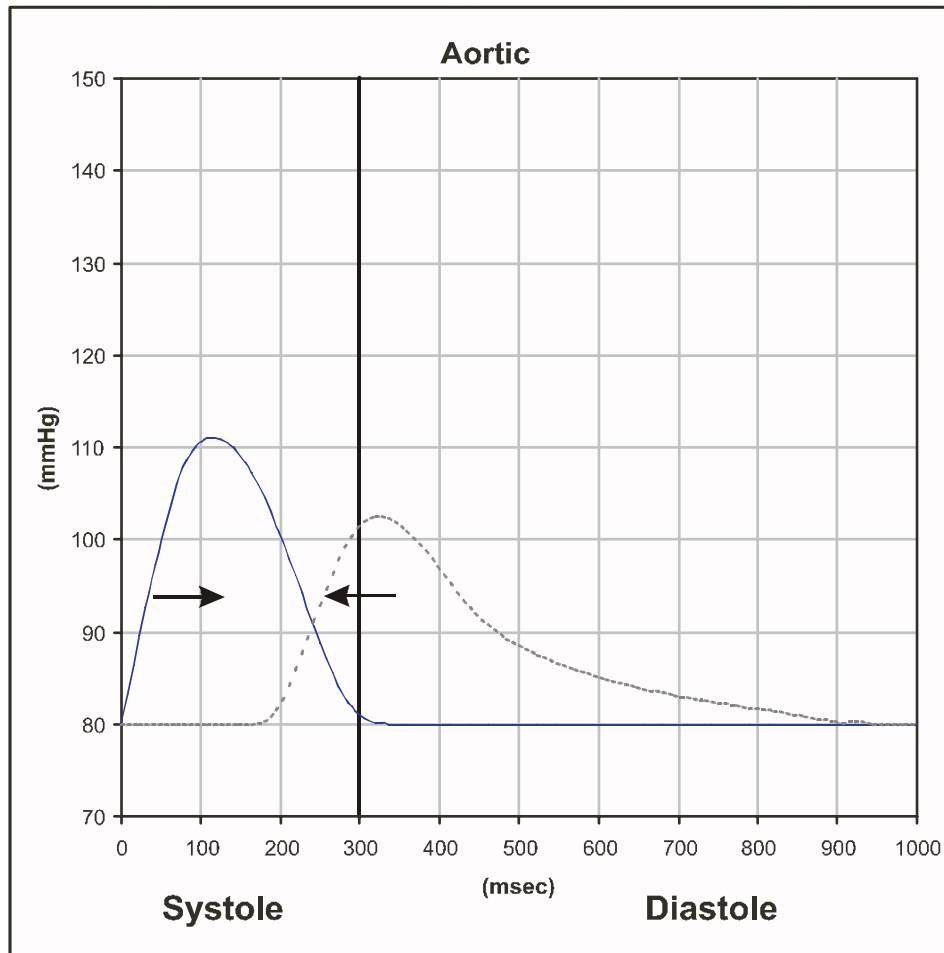


If the aorta was a long open-ended tube providing a simple resistance to flow (i.e., there was no wave reflection), then:

The pressure wave in the aortic **root** would show a single peak for each contraction.*

* All wave shapes represented are idealized

Pressure Wave Reflection at the Heart



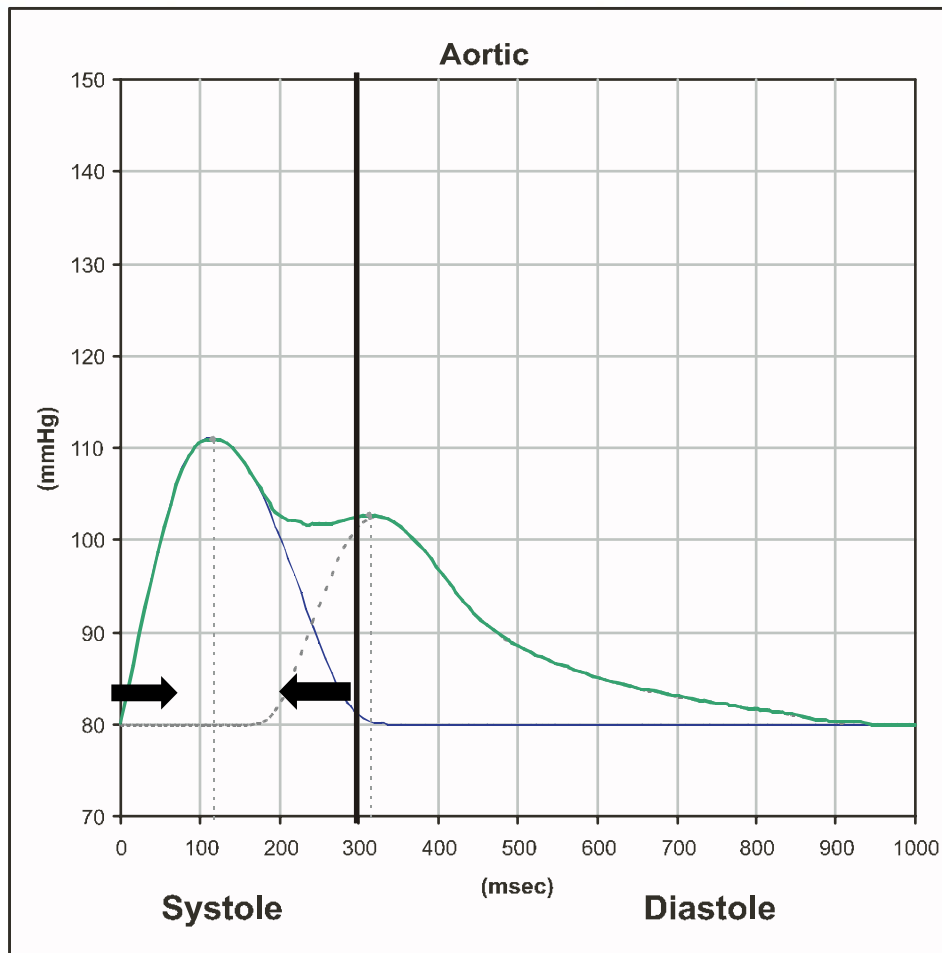
If we connect the network of arteries with all of its bifurcations and vascular beds, then

... as this primary wave travels along the arteries, it will generate **reflected waves*** from each bifurcation and from the peripheral vascular beds.

... all of these small reflected waves return to the heart, **summing to create a reflected wave as shown**, starting before the end of systole.

* Reflected waves are offset from baseline in this image

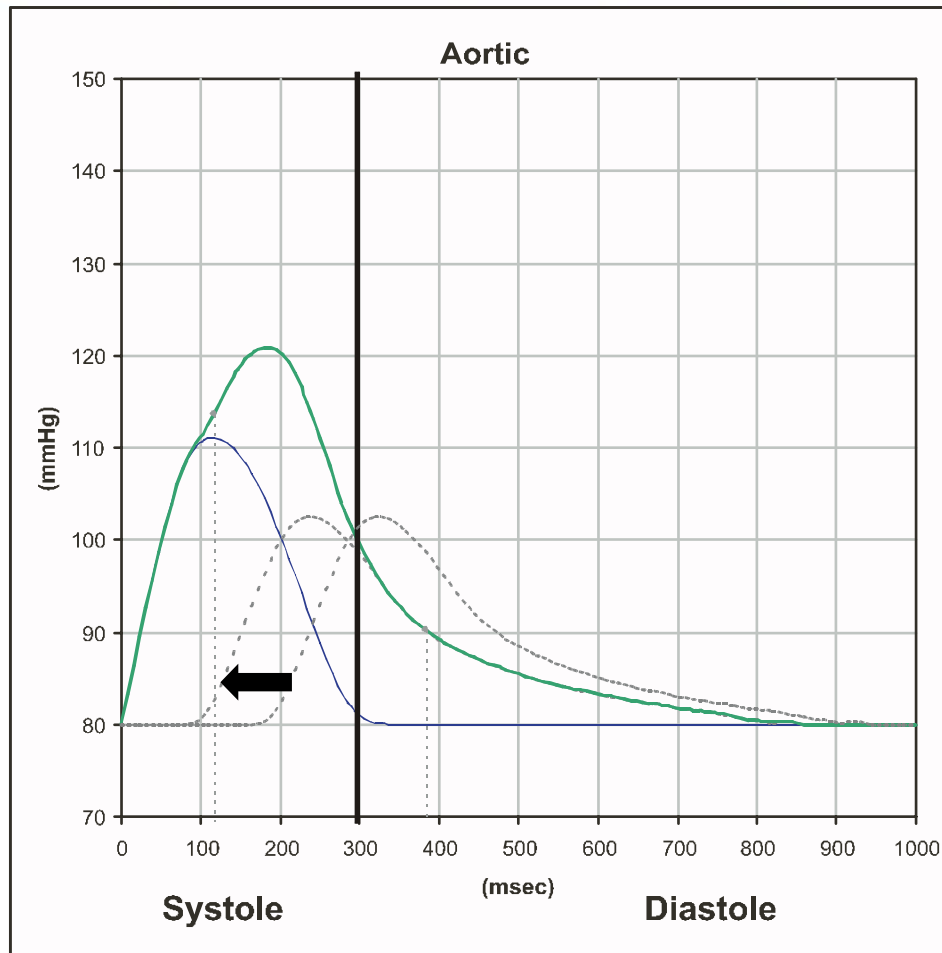
Pressure Wave Reflection at the Heart



Pressure in the aortic root is the sum of the outgoing and reflected wave (depicted by the green wave).

Note how the reflected wave boosts the coronary artery (aortic root) pressure during diastole when over 95% of perfusion of the myocardium takes place.

Pressure Wave Reflection at the Heart



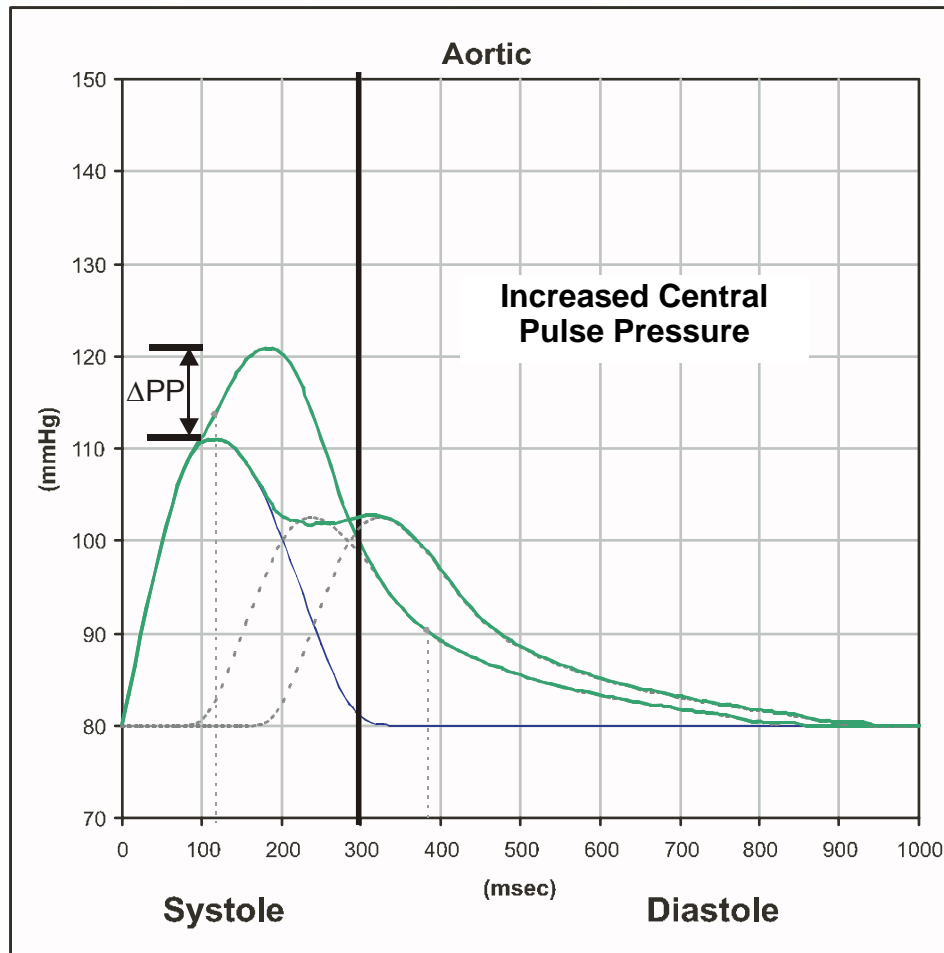
As the patient's arteries get stiffer...

then pulse wave velocity increases, and the reflected wave returns to the heart sooner.

Now, there is a very different aortic root pressure waveform (depicted by the green waveform).

As a result, there are **three** important clinical implications.

Pressure Wave Reflection at the Heart

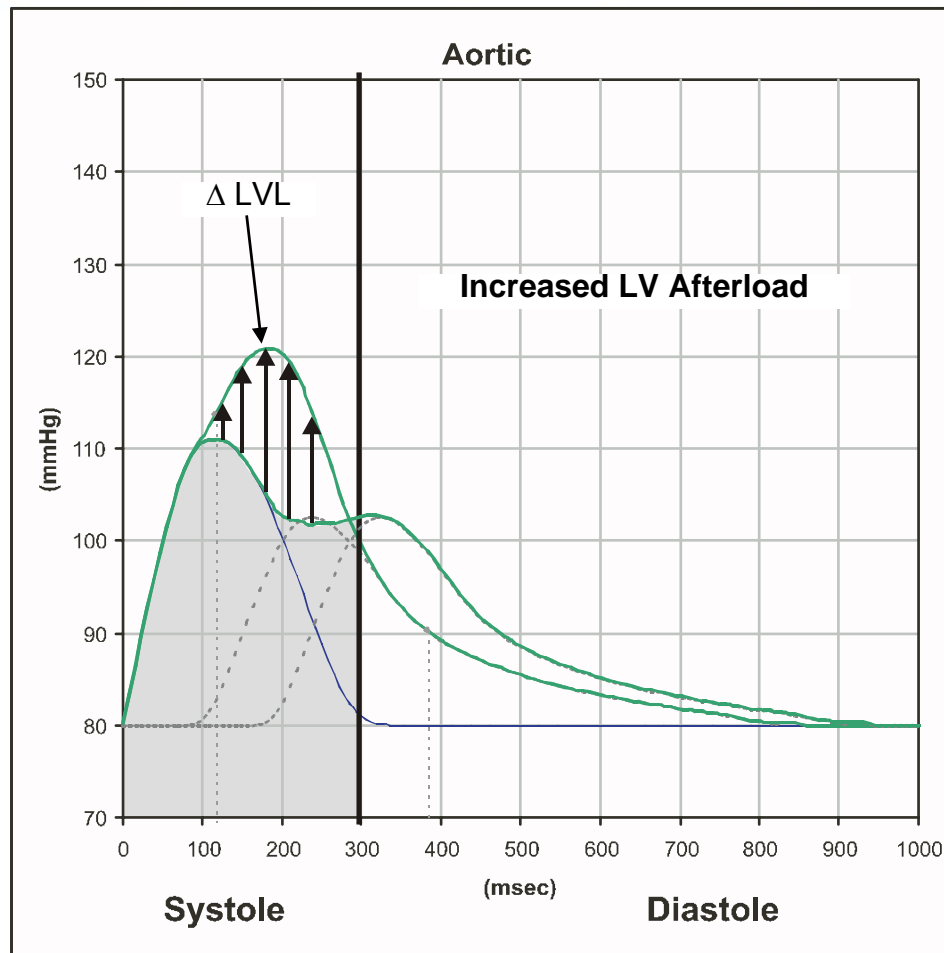


First, the **central systolic pressure** and **central pulse pressure** are increased.

An increase in the central pulse pressure increases the risk of cardiovascular disease.

NOTE: The magnitude of changes in central systolic pressure may be different than the magnitude of changes in brachial systolic pressure.

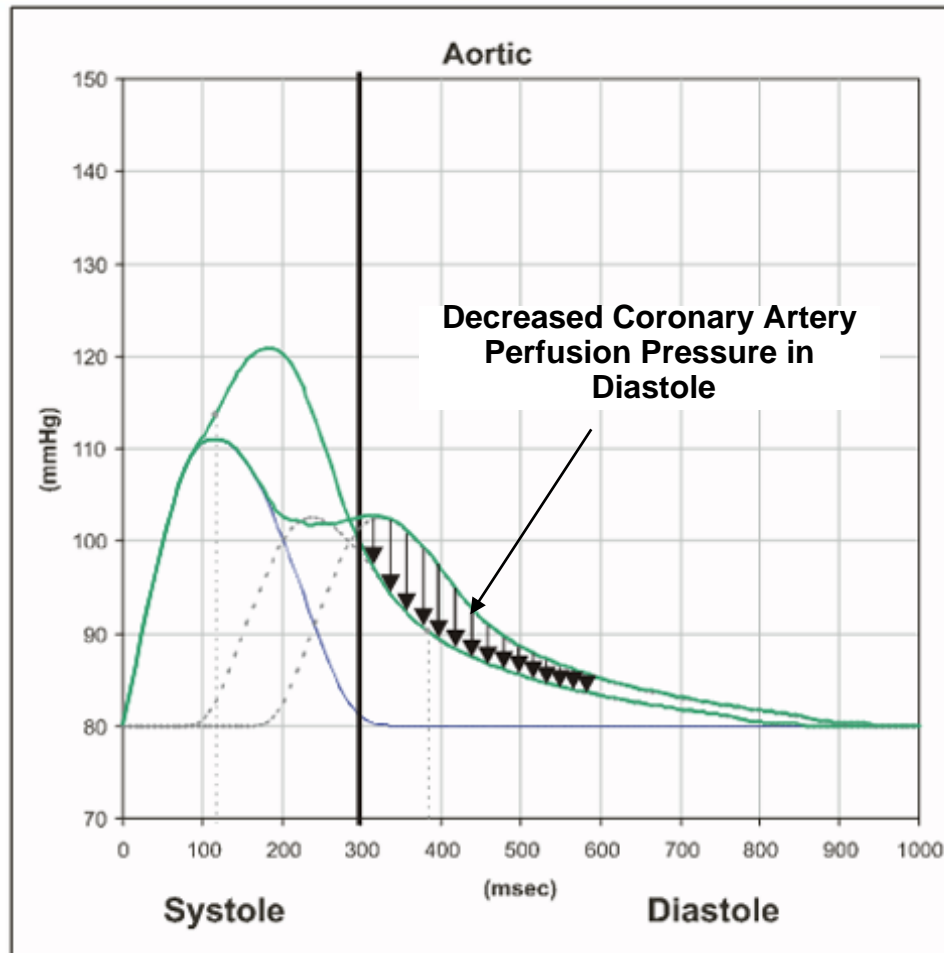
Pressure Wave Reflection at the Heart



Second, there is an **increase in left ventricular (LV) afterload.**

An increase in LV afterload accelerates increase in LV mass and **increases LV hypertrophy** (depicted by black arrows).

Pressure Wave Reflection at the Heart



Third, the pressure in the coronary arteries during the critical diastole period is reduced, **increasing the risk of myocardial ischemia.**

CONCLUSION:
Increased arterial stiffness has multiple and independent effects on the cardiovascular system.



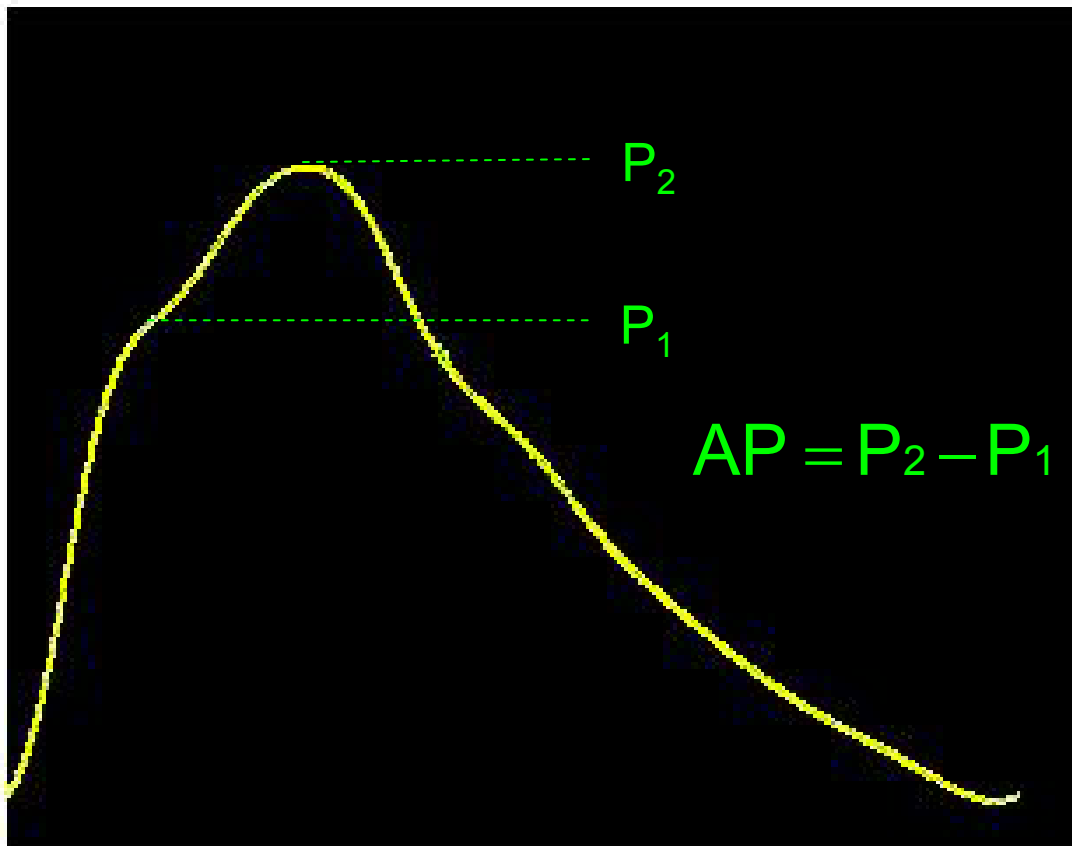
Pulse Wave Analysis Indices

Waveform Augmentation

As the arteries stiffen, the reflected wave arrives earlier in systole. Thus, it **augments** the left ventricular afterload.

- Consequently, the pressure against which the heart must pump increases when arteries stiffen
- Energy used by the heart to pump against this added pressure is wasted
- Young, healthy adults have more compliant arteries in which the pressure wave travels more slowly, delaying the occurrence of the reflected wave at the heart into diastole; as a result, young people often show no augmentation of systolic pressure

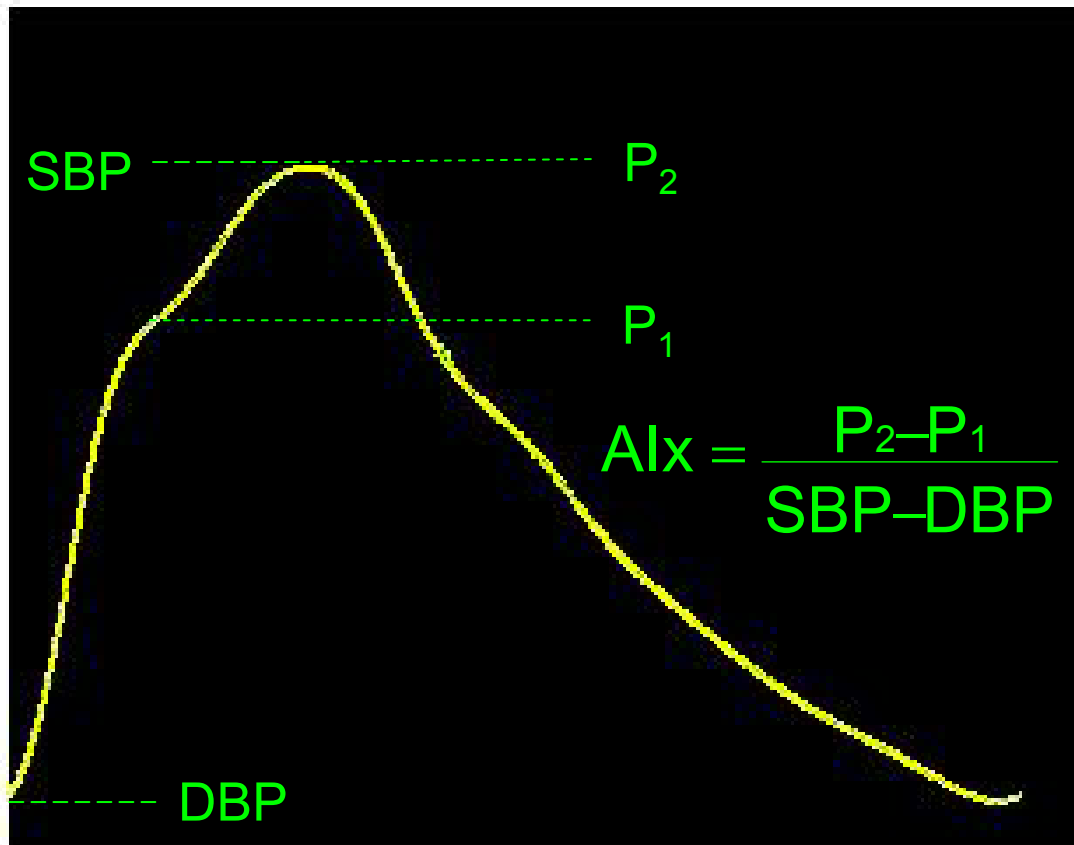
Augmentation Pressure (AP)



Augmentation Pressure :

- Calculated as $P_2 - P_1$
- P_1 corresponds to the incident pressure waveform during systole (generated by left ventricular contraction)
- P_2 is the reflected wave added to the incident waveform

Augmentation Index (Alx)



Augmentation Index (Alx):

- Calculated as AP divided by the Pulse Pressure (PP), typically expressed as a percentage
- Alx is a composite measure of the magnitude of wave reflection and arterial stiffness in all the conduit arteries which affects timing of wave reflection

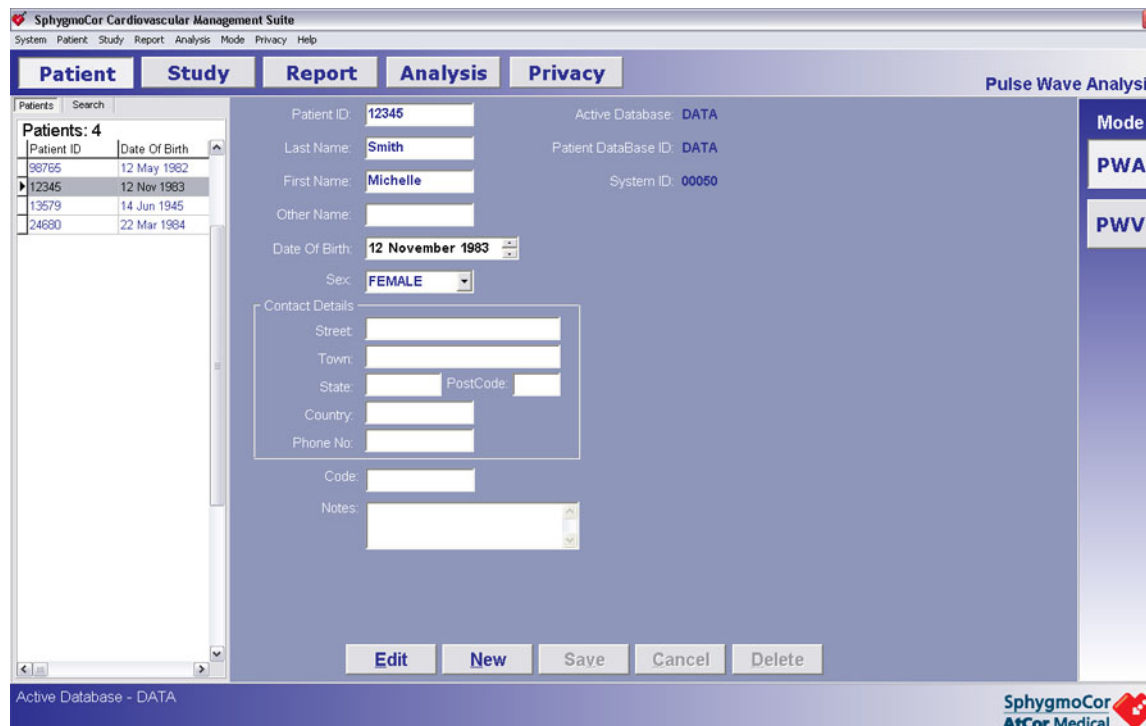
Importance of Augmentation

- Higher values of AP and AIx indicate increased wave reflection from the periphery and/or early return of the reflected wave as a result of **increased pulse wave velocity** (due to increased arterial stiffness)
- AIx has been shown to be an independent predictor of CV morbidity and mortality in ESRD patients, and significantly correlated to increases in cardiovascular risk, left ventricular mass, and diastolic dysfunction



SphygmoCor Patient Screen

Patient Screen – Layout



System Patient Study Report Analysis Mode Privacy Help

Patient Study Report Analysis Privacy

Pulse Wave Analysis

Patients: 4

Patient ID	Date Of Birth
98765	12 May 1982
12345	12 Nov 1983
13579	14 Jun 1945
24680	22 Mar 1984

Patient ID: 12345 Active Database: DATA

Last Name: Smith Patient DataBase ID: DATA

First Name: Michelle System ID: 00050

Other Name:

Date Of Birth: 12 November 1983

Sex: FEMALE

Contact Details

Street:

Town:

State: PostCode:

Country:

Phone No.:

Code:

Notes:

Edit New Save Cancel Delete

Active Database - DATA

SphygmoCor AtCor Medical

- Initial software screen in which existing patients can be selected or new patients can be created
- If applicable, system modalities are selected on the right
- *Note:* Patient information will be initially hidden upon opening the software program

Creating a New Patient

Patient ID: Active Database: **DATA**

Last Name: Patient DataBase ID: **DATA**

First Name: System ID: **00050**

Other Name:

Date Of Birth:

Sex:

Contact Details

Street:

Town:

State: PostCode:

Country:

Phone No:

Code:

Notes:

When creating a new patient, four (4) fields must be completed:

- Last Name: Entry can be as short as one character
- First Name: Entry can be as short as one character
- Date of Birth: Click on the day/month/year and use the numeric keys to update
- Sex: Choose the patient's gender from the drop down menu

Note: Completion of all other fields is optional

Patient Screen – Search

Patients | **Search**

Patient Search

Patient ID:

Last Name:

First Name:

Date Of Birth:

Search **Reset**

New

- Initiated by clicking on the 'Search' tab above the patient list
- Patients can be located via:
 - Patient ID
 - Last Name
 - First Name
 - Date of Birth
- Partial search parameters *will not* locate patients
- Not case sensitive
- Any or all fields can be used when searching

Patient Screen – Search Results

Patient ID	First Name
12345	Michelle
13579	John
24680	Andrea

Patient File Summary
 Smith, Michelle
 Number Of Studies: 4
 First Study: 26 Jan 2010, 10:18
 Last Study: 26 Jan 2010, 14:50
 Time Since Last Study:
 0 days

- If only one patient exists for the search criteria, the patient information is automatically selected and displayed in the center of the screen as well as in the Patient File Summary
- If multiple patients exist, a list appears under the Search button with the selected patient's information appearing in the Patient File Summary below the list
- Clicking on any patient within the list displays the selected patient's information in the center of the screen
- The 'Reset' button clears all search fields and hides all patient information



Performing Pulse Wave Analysis

Performing PWA



- A brachial blood pressure is used to calibrate the radial blood pressure waveform
- Standard office blood pressure guidelines should be followed
- Either arm may be used, however, perform both the cuff measurement and the PWA assessment on the same arm; the cuff blood pressure should be measured **prior** to a SphygmoCor assessment
- The patient should be in the same position throughout the brachial blood pressure and SphygmoCor assessment

Performing PWA

Height: 165 cm

Weight: kg

Body Mass Index: (kg/m²)

Operator:

Medications:

Notes:

Brachial

SP 144

DP 92

MP

- The patient should rest for approximately 5 minutes before the brachial blood pressure is taken
- Enter the brachial (cuff) systolic and diastolic blood pressure in the Study Screen of the SphygmoCor software
- Height is required if 'Vascular Reference Age' calculation is desired*
- Click 'Capture Data' to initiate the assessment

**Note: Height and Weight settings can be displayed in either metric or imperial values*

Positioning – Operator and Patient

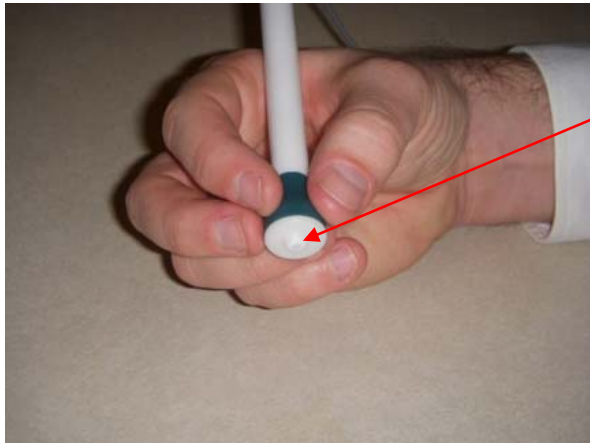


Proper Hand Positioning

Successful central blood pressure measurements are obtained through proper positioning of the operator and patient.

- The operator should be seated, facing the patient, alongside a firm surface (eg, table, desk, etc.)
- The elbow and forearm of both the patient and operator should be resting on the surface
- The operator should use his/her opposite hand (not used to hold tonometer) to support and slightly bend the patient's wrist

Locating the Pulse



The tonometer contains a pressure sensing element (very small gray dot at the tip) – precise placement of this element over the strongest pulse point is an important starting point during PWA measurements.

When palpating the radial pulse, gently feel for the strongest pulse point of the patient's radial artery.

Once the strongest pulse point has been palpated:

- Slowly lift fingertip from pulse, looking for visual reference mark on the skin (eg, hair follicle, birthmark, vein)
- Keep your eye trained on this spot while moving tonometer next to wrist
- Visually connect the gray tip of the tonometer onto the reference mark (roll the tonometer over top)
- Assume proper tonometry positioning

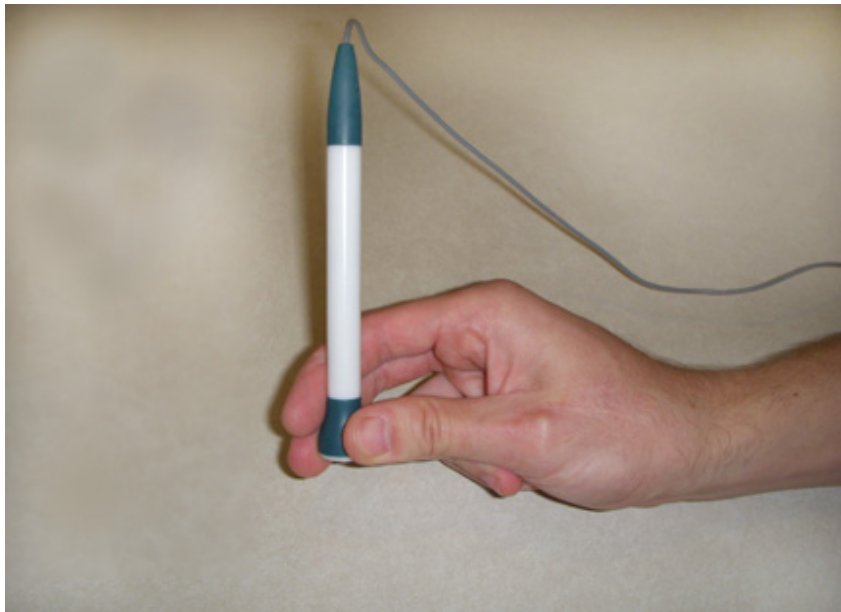


Tonometer Placement

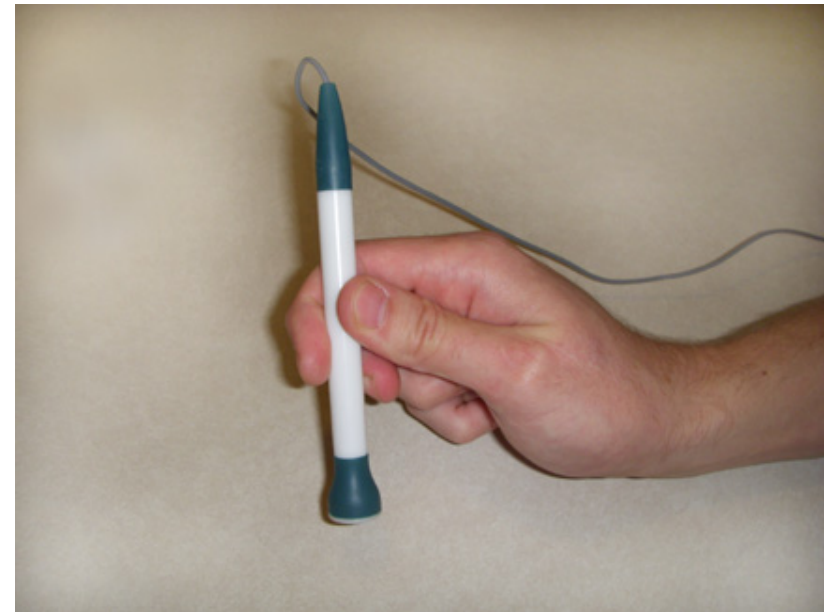
Holding the Tonometer

The tonometer should be held at the base so that the operator's fingertips make contact with the patient's skin.

Holding the tonometer higher on the shaft will allow less control and makes data capture more difficult.



Correct Grip



Incorrect Grip

PWA Study Capture Screen

The PWA Study Capture Screen is comprised of two windows:

- The top, larger window represents 5 seconds of data capture
- The bottom, smaller window represents 10 seconds of data capture
- A total of 10 seconds of consistent, quality waveform data is required to complete the assessment

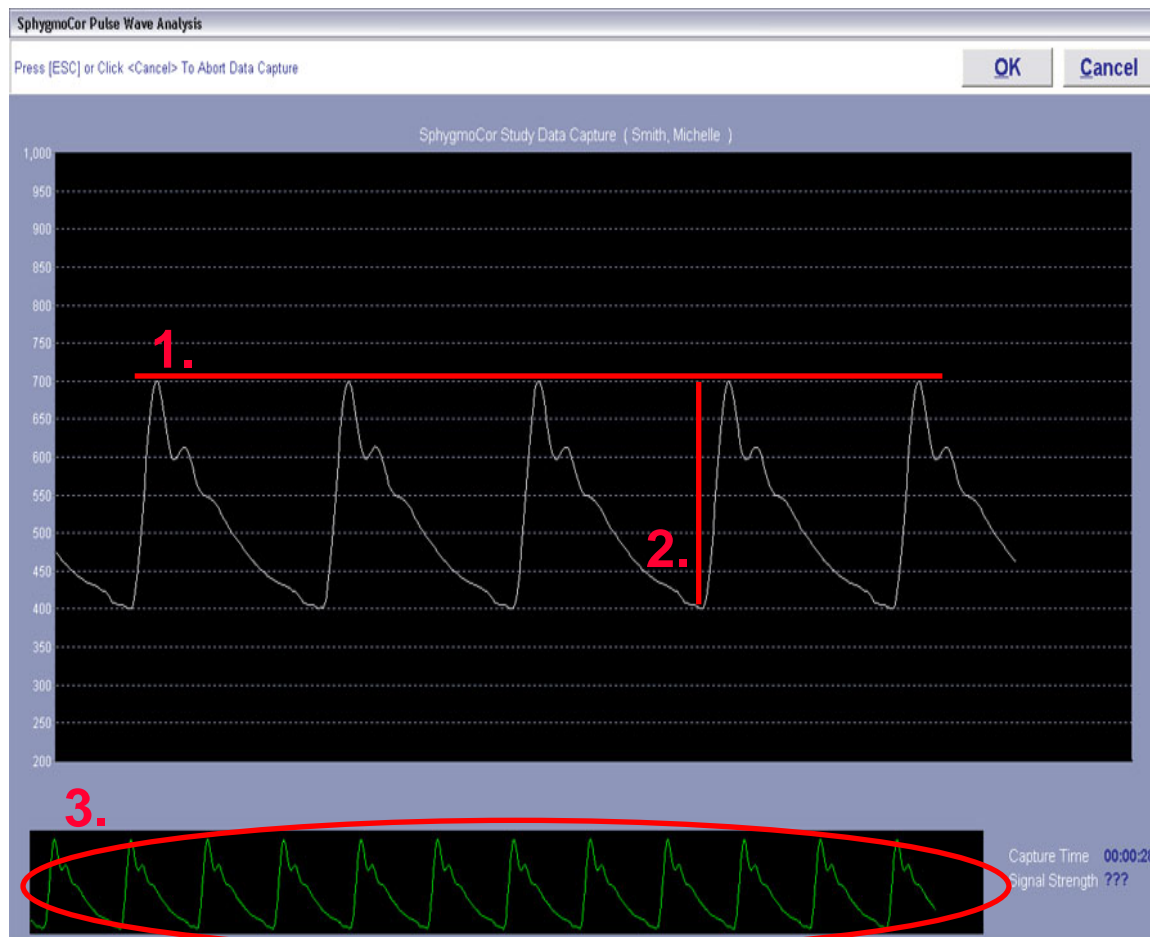


Successful Waveform Acquisition

High quality data requires that the following conditions be satisfied:

1. Consistent Pulse Height
2. Large Waveform Amplitude (filling as much of the screen as possible)
3. Consistent waveform shapes for ten seconds

Note the lack of artifact and “noise” in the signal



PWA – Capture Guide

SphygmoCor Configuration

Quality Control

Minimum Pulse Height:

Maximum Pulse Height Variation:

Maximum Diastolic Variation:

Pressure Sensitivity

Upper Limit:

Measurement Units

Metric Imperial

Tonometer Serial Number

Comms Port

Clinical Report

Augmentation Index

Augmentation Index @ HR75

Capture Guide

Guidance Bars

Auto Capture

Save **Cancel** **Set Defaults**

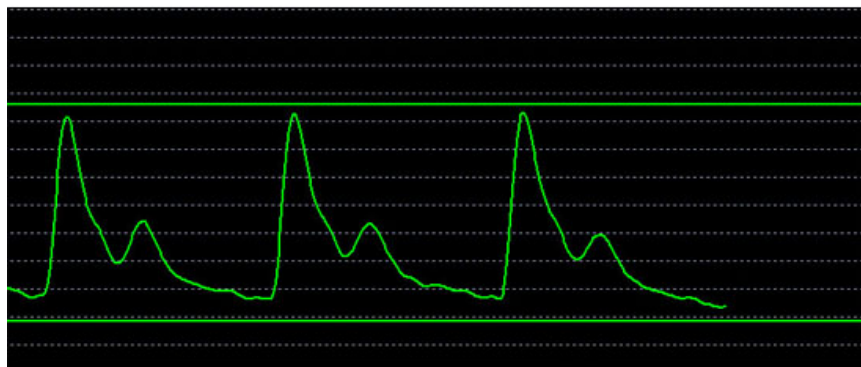
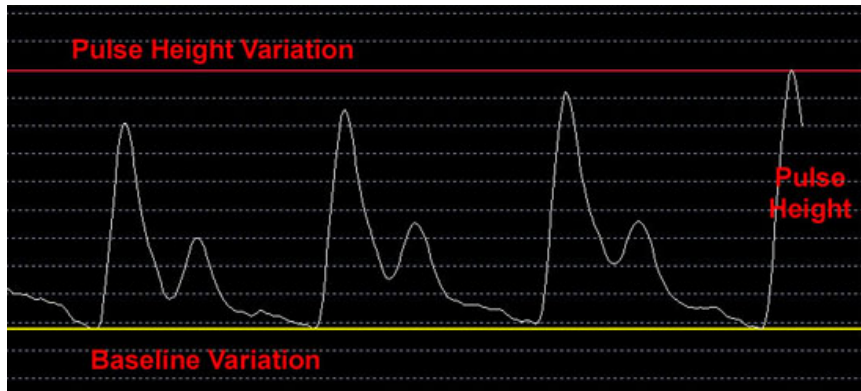
- Capture Guide provides instant feedback during waveform acquisition
- Capture Guide has two options:
 - Guidance Bars
 - Auto Capture
- Capture Guide settings are enabled through the SphygmoCor Configuration window found under System on the toolbar of the Patient Screen

Note: Manual capture is still possible if Capture Guide is disabled

PWA – Capture Guide Feature

- Guidance Bars provide visual, color-coded feedback to the operator in real time regarding parameters associated with meeting the minimum Quality Control criteria
- Guidance Bars provide feedback regarding:
 - Pulse Height Variation
 - Baseline Variation
 - Pulse Height
- Once a waveform appears, the software automatically displays a horizontal bar at the base and peak of the waveform as well as a vertical bar on the right side of the waveform window

PWA – Capture Guide Feature



Reduce Pulse Height Variation Reduce Baseline Variation
Increase Pulse Height

- The bars are color-coordinated using red, yellow and green
- Pulse Height Variation & Baseline Variation
 - Red indicates a variation greater than 10%
 - Yellow indicates a variation between 5 – 10%
 - Green indicates a variation less than 5%
- Pulse Height:
 - Red indicates a height less than 75
 - Yellow indicates a height between 75 – 85
 - Green indicates a height greater than 85
- Messages regarding tonometer adjustment are also displayed at the bottom of the screen

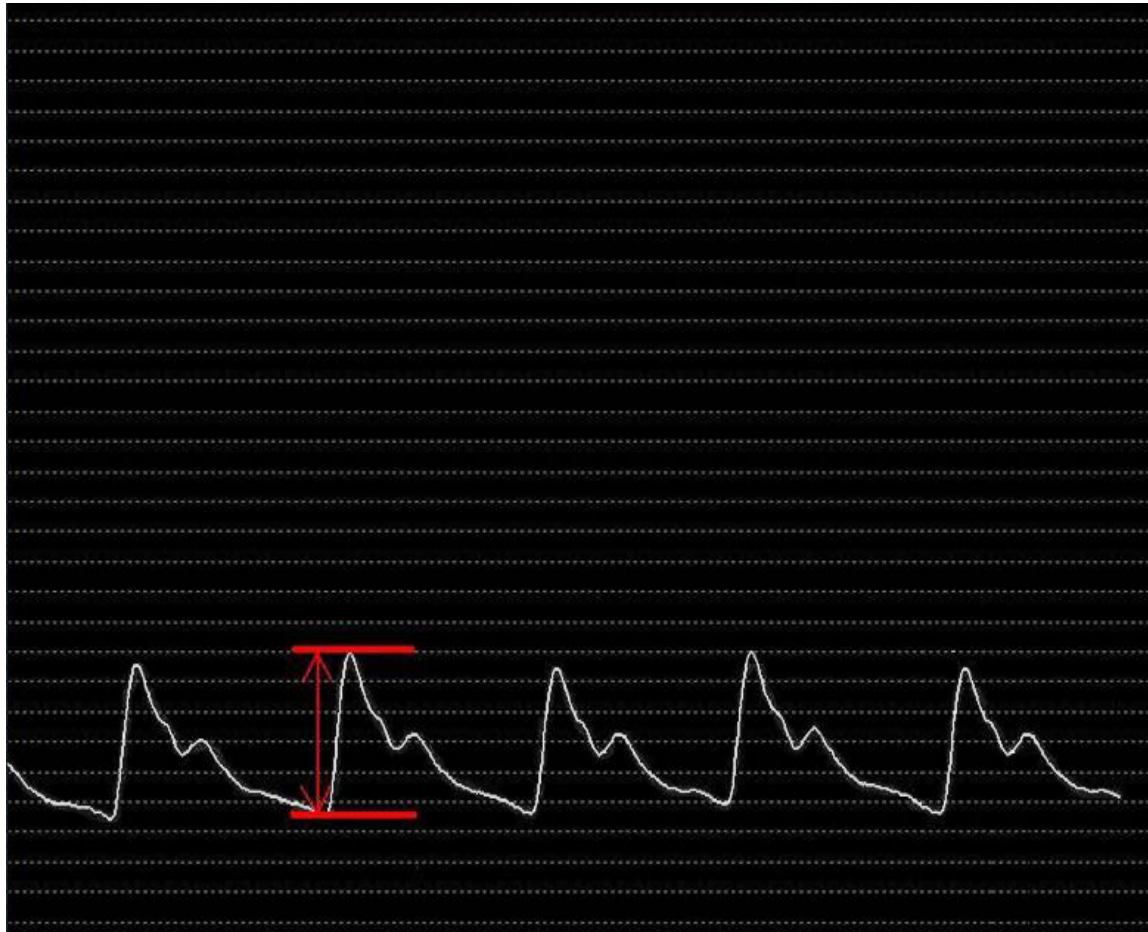
PWA – Capture Screen

- The Guidance Bars change colors with tonometer adjustments
- Once all bars become green and a consistent waveform is present, the waveform becomes green indicating that the quality criteria have likely been met
- With Auto-Capture enabled, the software automatically 'captures' or ends the assessment and advances to the report screen
- The keyboard spacebar can be pressed to manually capture the assessment



Note: the last two (2) seconds of data are discarded when manually capturing the assessment

Successful Waveform Acquisition



If the waveforms appear small:

- Wait until the signal scale is amplified as the signal reaches the right side of the screen
- Press slightly harder to induce stronger signal
- Adjust the tonometer positioning slightly so that the tip is over the strongest pulse point

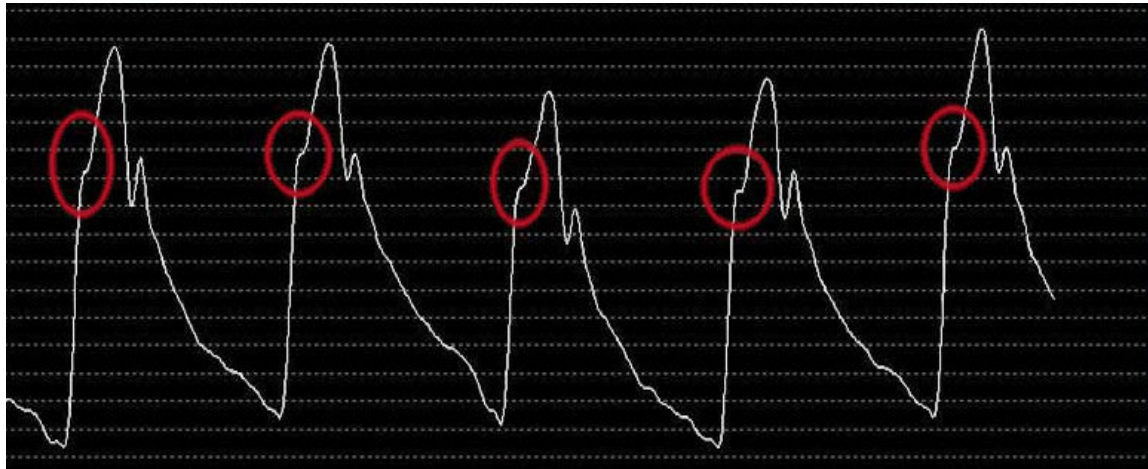
Successful Waveform Acquisition



Pulse height inconsistency is most commonly caused by either inconsistent hold-down pressure or respiratory variation.

- Hold tonometer at the base with fingers touching the patient's skin
- Ensure hand positioning is stable to maintain consistent hold-down pressure

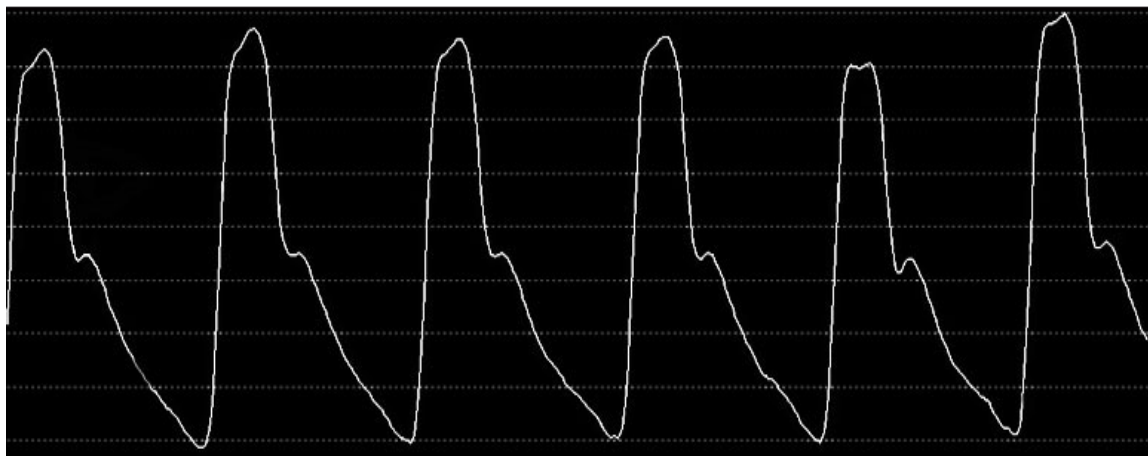
Successful Waveform Acquisition



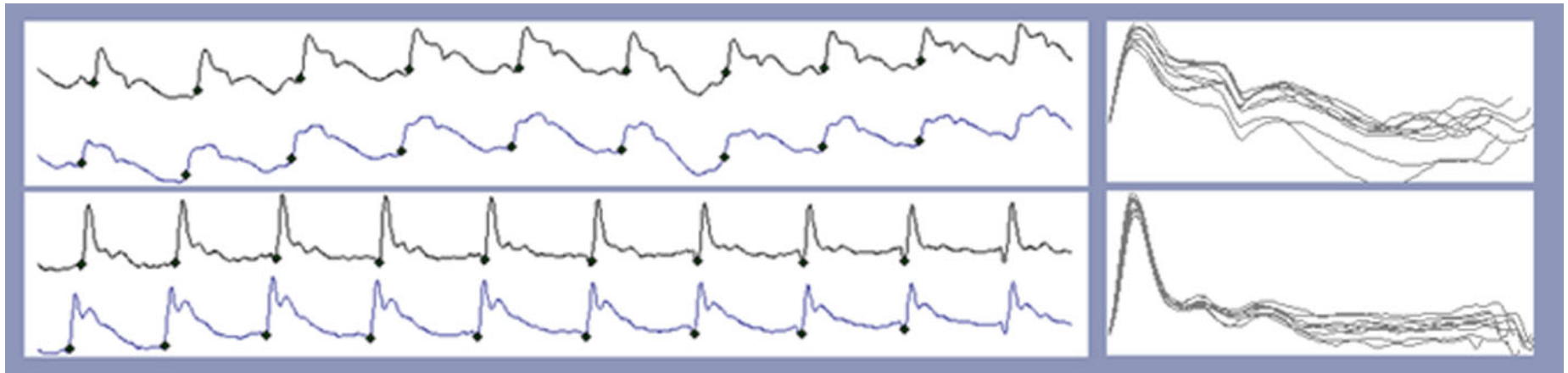
The initial upstroke of the waveform signal should be sharp from base to peak.

Improper tonometer positioning creates an inflection in the upstroke.

- Change the angle at which tonometer is held over the patient's pulse
- Adjust the location of the tonometer's tip



Successful Waveform Acquisition



Waveforms should be smooth without baseline “noise” in the signal. The diastolic portion should have a continuously decreasing curve. If the baseline signal is ‘noisy’ or has a flat diastolic curve, consider the following:

- Re-palpate the artery to find a more defined, stronger pulse point
- Try different angles and hold-down pressure of the tonometer until the signal improves

Patient Information
 Smith, John
 Patient ID:
 Birth Date: 15 Oct 1955
 Age: 54 Sex: MALE

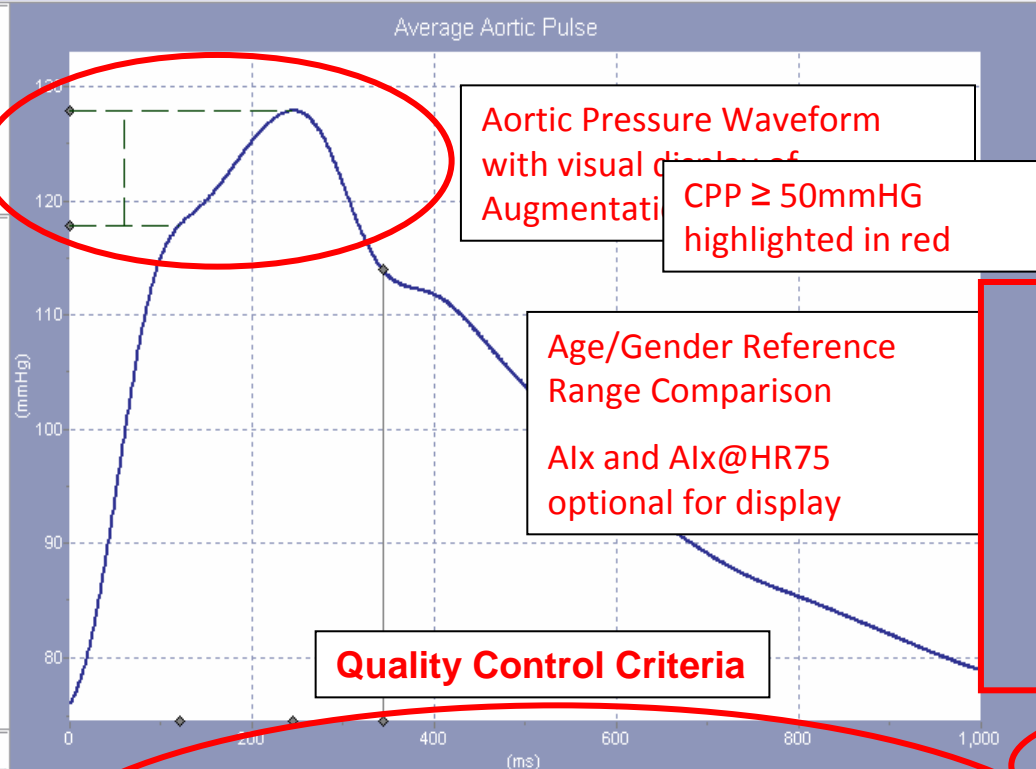
Study Information
 Operator:
 Height, Weight (BMI):
 5ft, 9in, 165lb (24.49 kg/m²)
 Medications:
 |

Notes:
 |

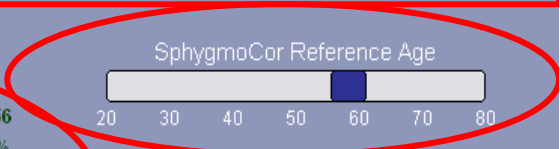
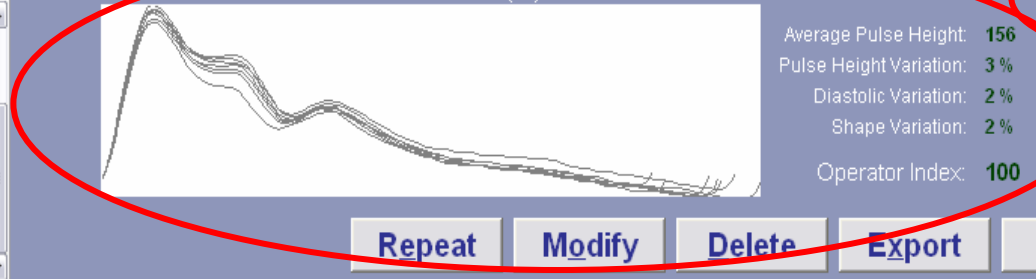
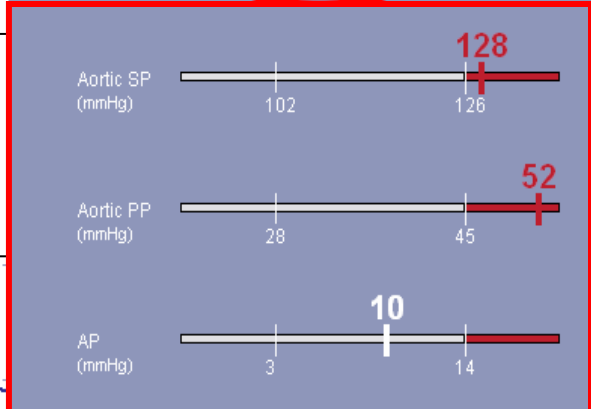
Interpretation:
 |

Assessment 5 of 5

Study Time
 20 Aug 2009, 21:09:07
 20 Aug 2009, 21:12:09
 11 Dec 2009, 13:23:23
 02 Mar 2010, 19:30:13
 ▶ 02 Mar 2010, 19:30:45



Aortic		Brachial	
128	SP	145	
76	DP	75	
99	MP	99	
52	PP	70	



SphygmoCor Reference Age

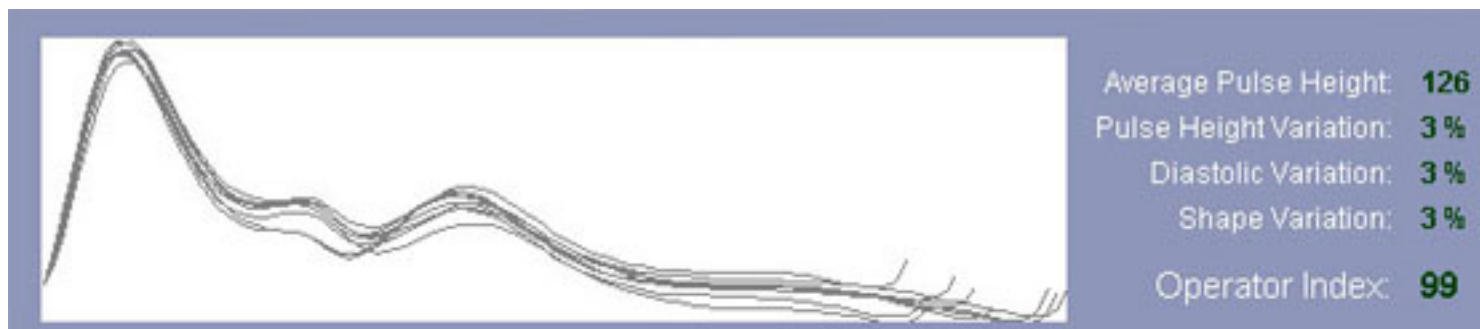
Repeat Modify Delete Export Print

Quality Control

The SphygmoCor System provides a number of indices that give information on the **quality and reproducibility** of the pulse waves captured. As a report is produced based on this data, it is important that all Quality Control criteria are met.

There are three sections related to Quality Control:

- 1) Pulse Overlay
- 2) Quality Control Indices
- 3) Operator Index

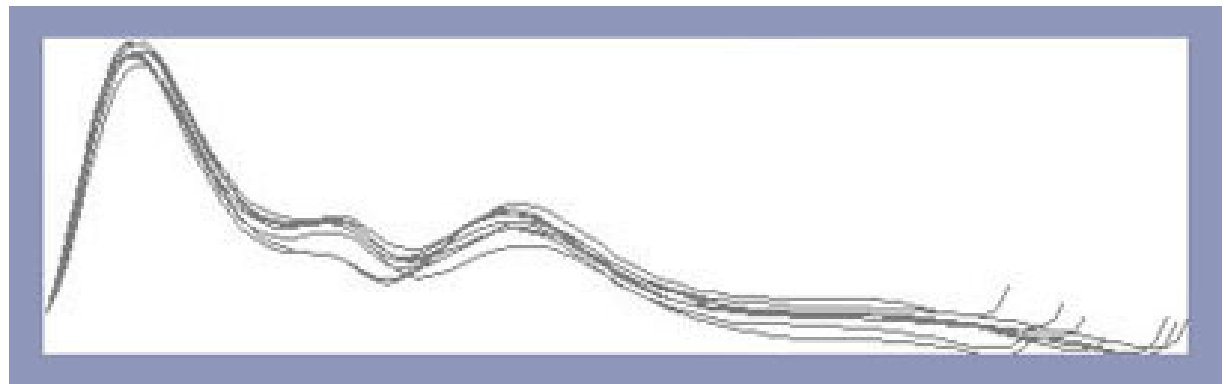


Quality Control – Pulse Overlay

Pulse Overlay

This area displays a visual guide as to how well the individual pulses can be overlaid to form an averaged pulse.

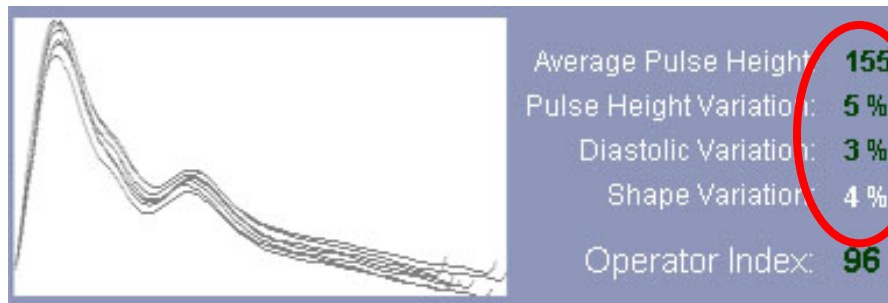
Ideally, there should be very little variability so that the overlay looks like one dark line.



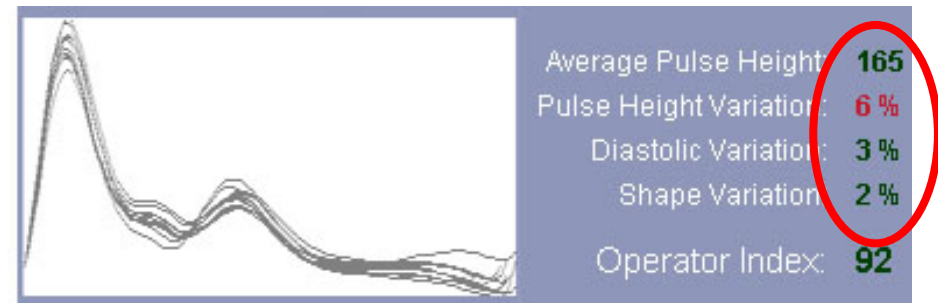
Quality Control – Indices

Examine the Quality Control Indices

- Acceptable values will appear in **GREEN** or **WHITE**
- Values outside of the acceptable range will appear in red
- If any red values appear, the assessment should be repeated



Acceptable

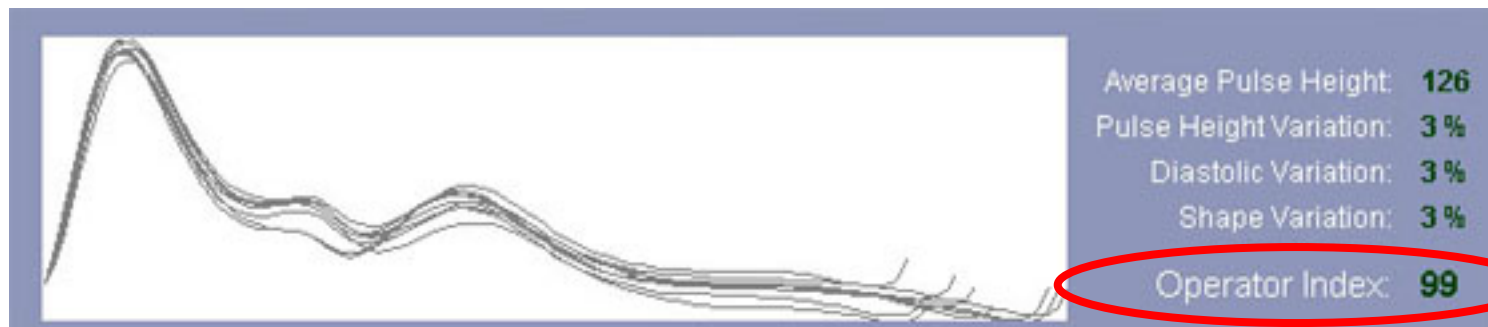


Unacceptable

Quality Control – Operator Index

Operator Index

- The Operator Index is a number calculated from the four Quality Control Indices. It is calculated by assigning a weight to each of these variables to determine a combined number as a percentage
- This parameter is indicative of operator reproducibility and should be a score of 80 or higher. An Operator Index below 80 should be repeated to obtain a more reproducible waveform





Pulse Wave Velocity

Pulse Wave Velocity

Pulse Wave Velocity (PWV) is the speed of the pressure wave travelling through the arteries.

PWV is calculated by the formula:

$$\text{PWV} = \text{distance (m)} / \text{transit time (s)}$$

Aortic PWV is a direct measure of the arterial (aortic) stiffness.

- Aortic stiffness is a subset of arterial stiffness (arterial stiffness refers to stiffness in any section of the conduit arteries, including the aorta)

Pulse Wave Velocity – Gold Standard

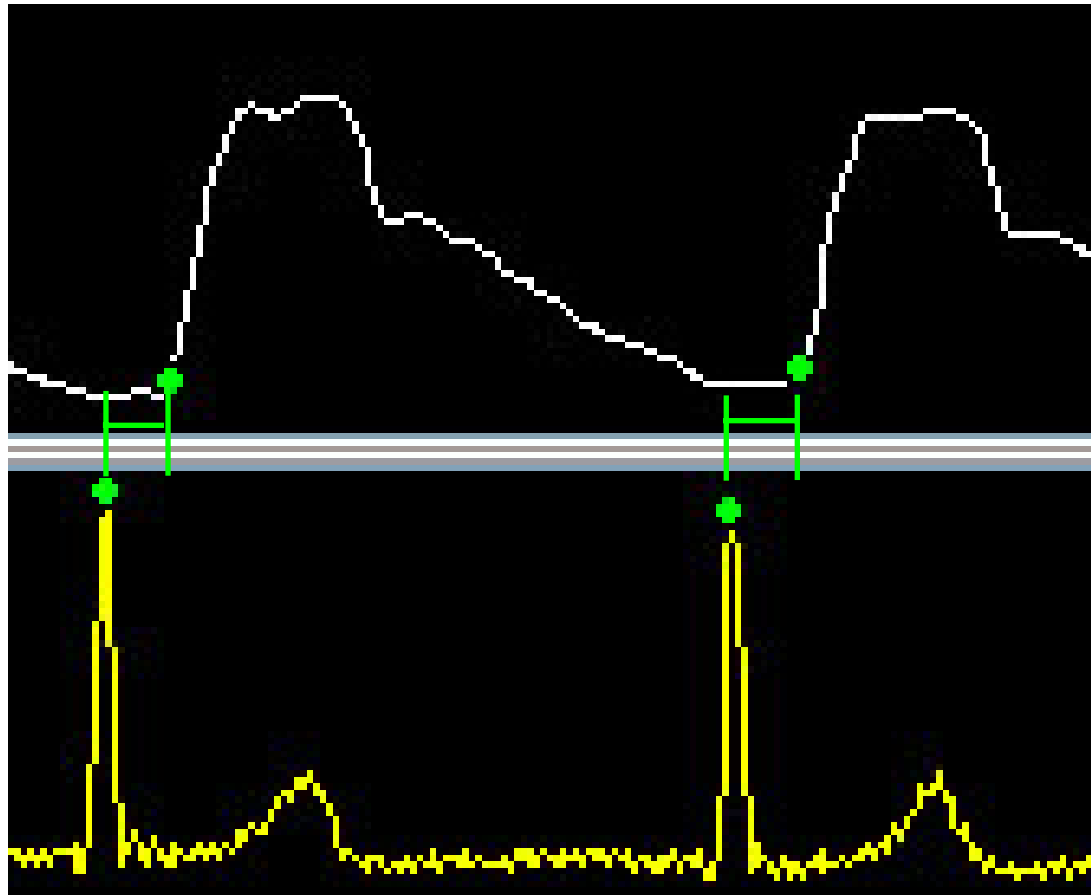
Carotid - femoral is most commonly measured as it is considered to represent aortic PWV. The stiffer the aorta, the higher the aortic PWV.

- A highly compliant aorta has a relatively low PWV (~ **6 m/s**) and a very stiff aorta results in a much higher PWV (~ **14 m/s**)
- Aortic PWV has also been shown to be a significant and independent marker of the risk of cardiovascular disease, including coronary artery disease, congestive heart failure and fatal stroke
- Aortic PWV has also been associated with the risk of non-CV diseases, such as:
 - ESRD
 - Moderate chronic kidney disease
 - Rheumatoid arthritis
 - Systemic vasculitis
 - Systemic lupus erythematosus

Pulse Wave Velocity Calculation

Pulse Wave Velocity is calculated using the pressure waveforms from the carotid and femoral arteries and a 3-lead ECG.

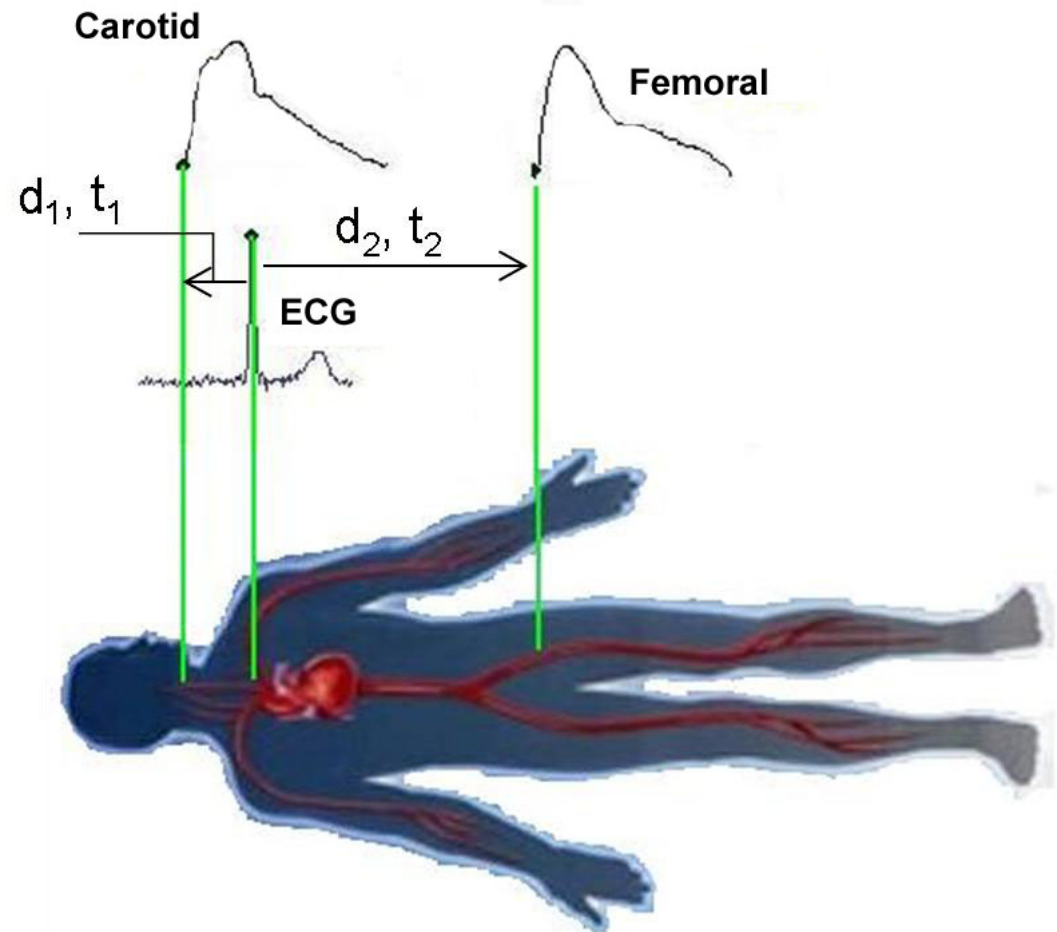
The time delay between the R-wave of the ECG and the foot (initial upstroke) of the pressure waveform is used in calculating the measurement.



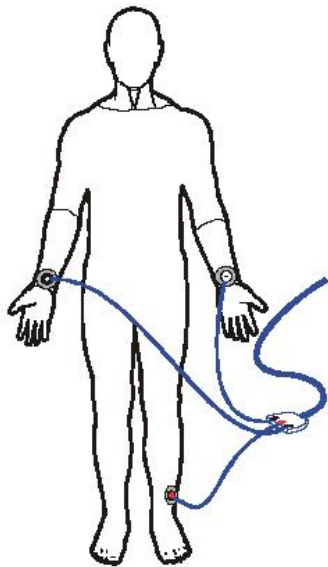
Pulse Wave Velocity Calculation

When the heart beats, the pressure waves travel simultaneously in opposite directions. To obtain PWV of the aorta, measurements are taken using the carotid and femoral pulse points.

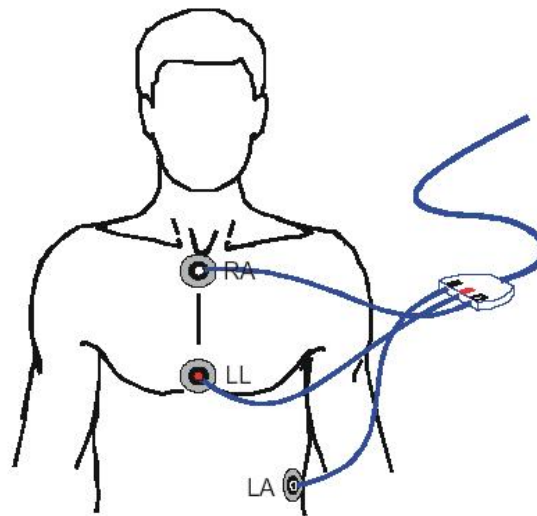
$d_2 - d_1 =$ Distance traveled (D)
 $t_2 - t_1 =$ Time taken to travel D(T)
 Velocity = D/T



PWV Recording – Positioning



Electrodes on Peripheral Limbs



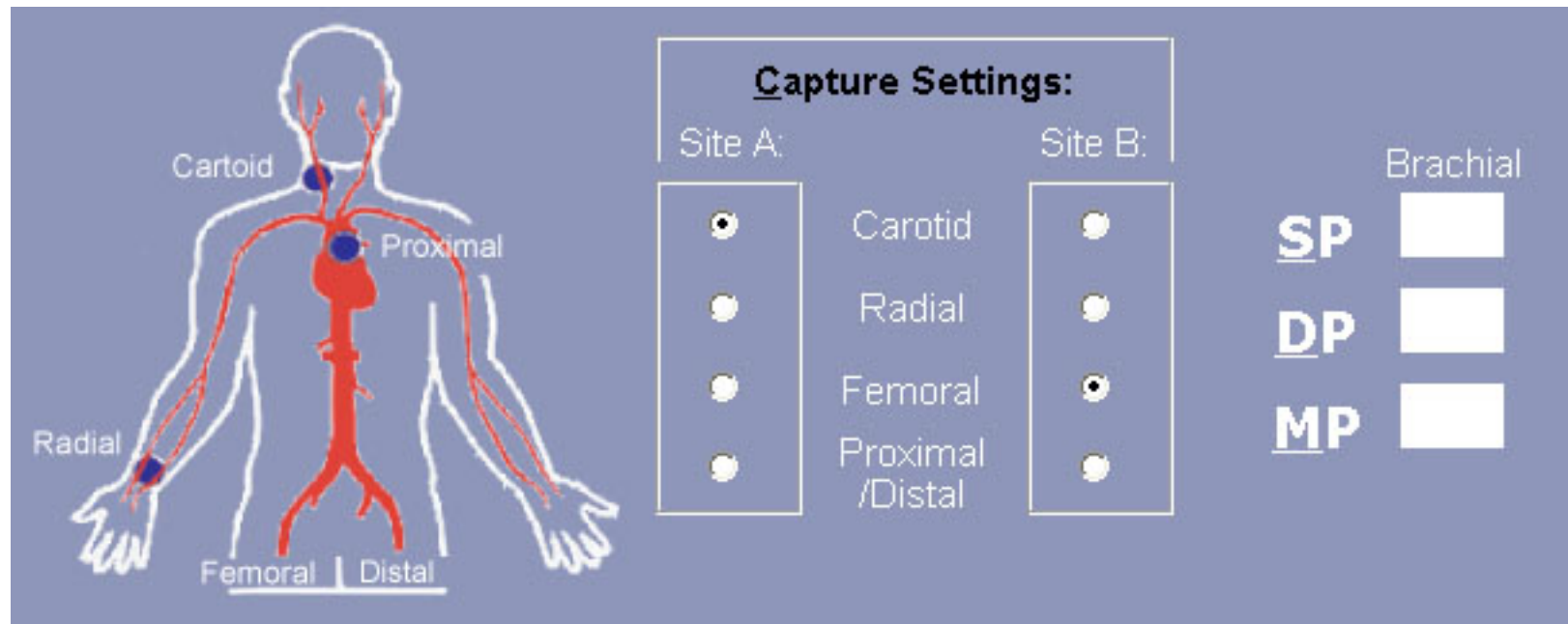
Electrodes on Chest

The patient should be lying **supine** with his/her arms positioned alongside the body.

To ensure a stable and artifact-free ECG, the electrodes must be positioned correctly. Electrodes may be placed on the limbs (LL, LA, RA), or on the chest if needed to obtain a stronger signal.

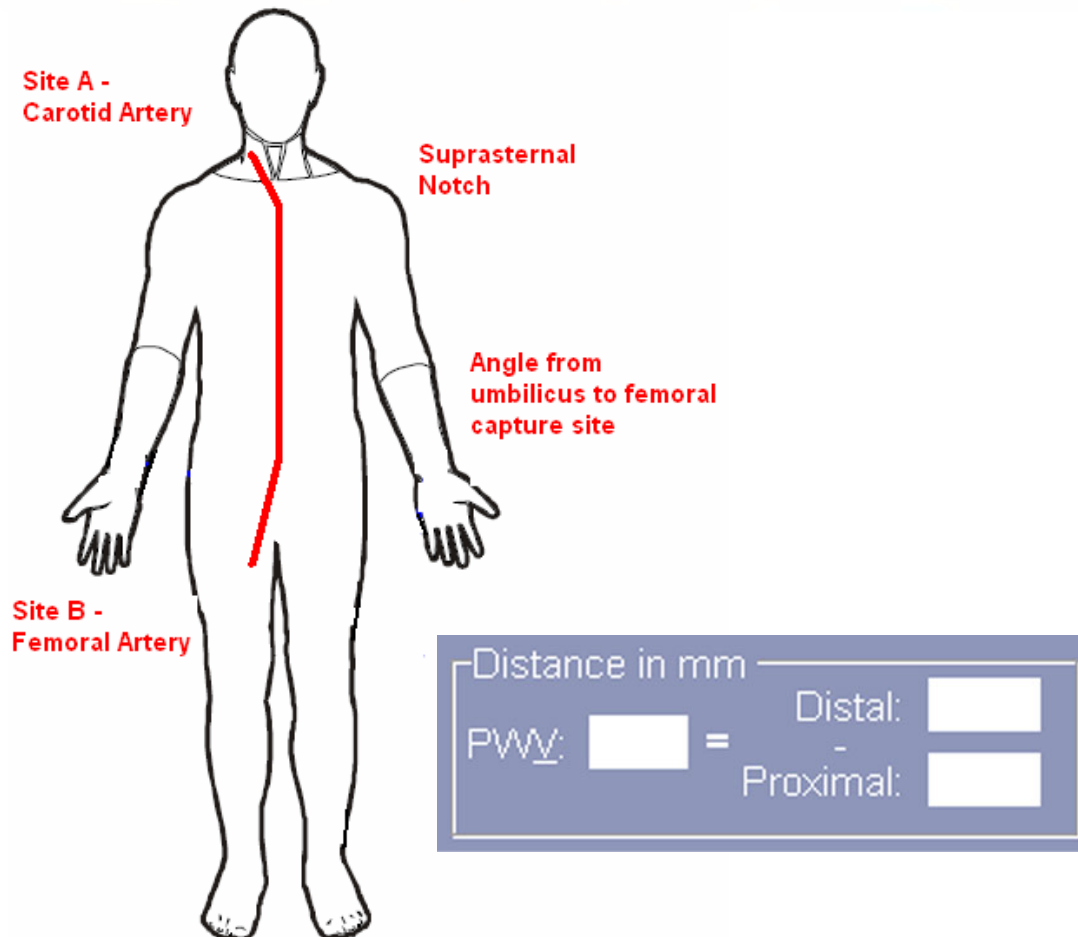
The SphygmoCor system utilizes a **3-lead ECG** in a modified LEAD II configuration.

PWV Study Screen



- Carotid and Femoral captures sites are the default settings for measuring pulse wave velocity
- Enter the patient's brachial blood pressure

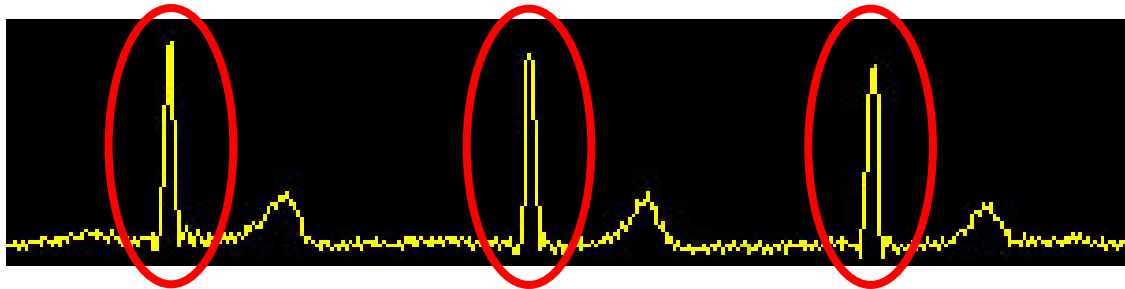
Measuring Distances



- Measure the distance from the center of the suprasternal notch to the carotid (or proximal) site and enter that value in millimeters in the 'Proximal' site box
- Measure the distance from the center of the suprasternal notch to the femoral (or distal) site (tracing the arterial path to the umbilicus, then angled toward the femoral pulse) and enter that value in millimeters in the 'Distal' site box
- The software calculates the distance used in the PWV calculations and automatically display it in the PWV box
- The choices for Capture Times can be adjusted if desired

Recording PWV

Ensure that a quality ECG signal is present prior to performing the tonometry measurements. The R-wave should be the tallest signal.



For PWV, a steady baseline in tonometer readings is not essential, however, it is still important to have a waveform that has a clearly defined '**foot** of the wave.'

Once data for Site A has been captured, data for Site B can be captured.

Recording PWV – Carotid Measurement

Carotid measurement:

- Remove pillow if one is present (a towel under the patient's neck may be used, if needed); the patient's head should be tilted slightly back and to one side (either left or right)
- The operator should palpate for the strongest pulse point and place the tonometer directly on the top of the skin at this point
- The tonometer should be held perpendicular to the plane of the neck to take advantage of ligaments in the neck to stabilize the artery
- The operator can be standing either behind the patient's head or to one side, however, stability of the operator's arm is required

Recording PWV – Carotid Measurement



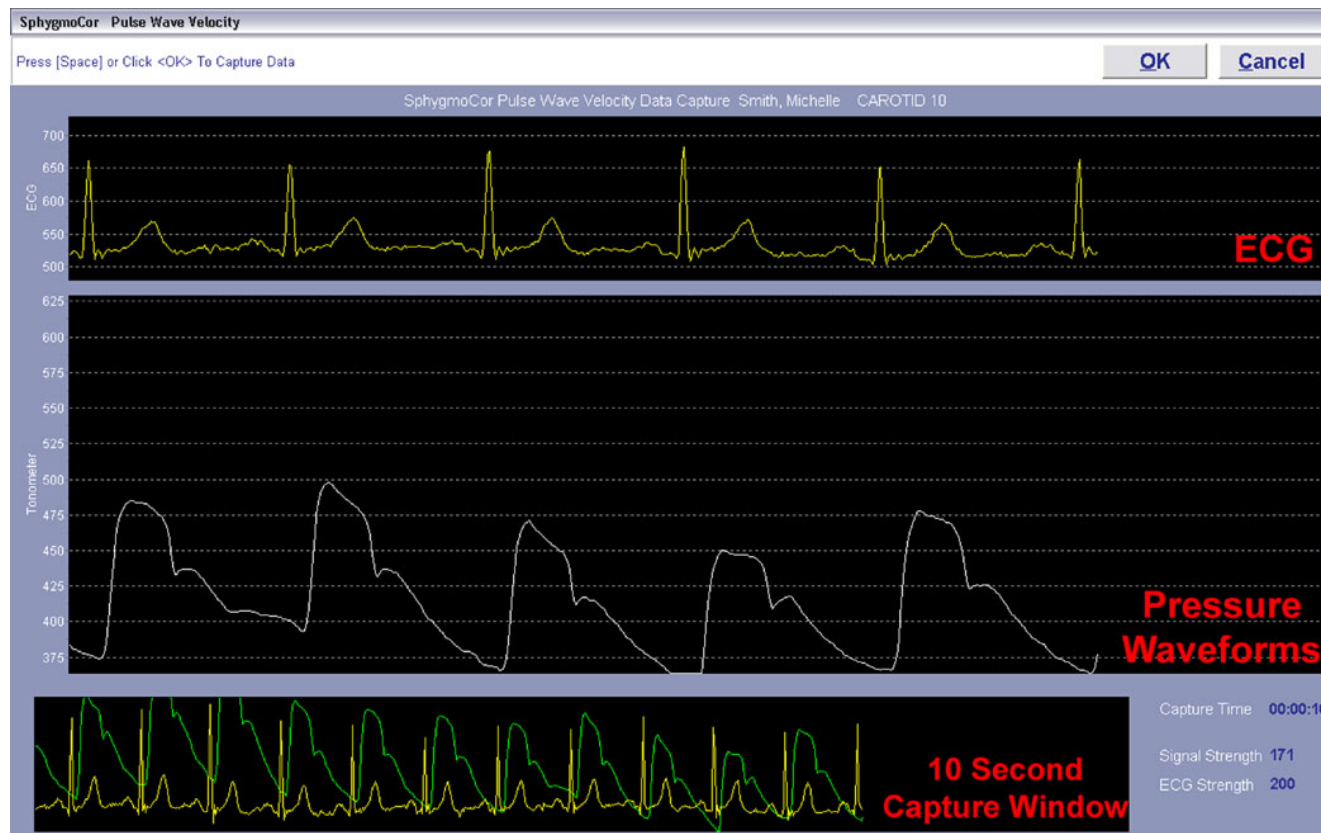
Recording PWV – Femoral Measurement

Femoral measurement:

- The patient's thigh (flexed at the hip joint) should be rotated away from the midline of the body
- The femoral pulse is best felt by pressing down at a point that is midway between the anterior superior iliac spine and the front of the pubic bone



Recording PWV – Capture Screen



- A horizontal tracing and an ECG signal are displayed
- Check the quality of the ECG signal and adjust electrodes as needed until a clear signal with a distinct R-wave is displayed
- Obtain a waveform recording from Site A
- When an acceptable reading has been obtained, press the Space bar on the computer keyboard, and repeat steps for Site B

Pulse Wave Velocity Report



PWV Quality Control

Site A-B	MeanT(ms)	SD(ms)	N	HR(bpm)
ECG-CAR	62.2	2.1	11	78
ECG-FEM	113.1	0.8	9	79
CAR-FEM	50.9	2.2		

CAR-FEM PTT SD	4.4 %
Pulse Wave Velocity (m/s)	10.8 ± 0.5

1. Both Standard Deviations (SD) should be 6% or less of the Mean Time. If this criteria is met than the result will be displayed in **Green**. If the SD is more than 6%, the result will be displayed in **Red**.
2. The heart rates (HR) should be within 5 beats per minute (BPM) of each other (see next slide).
3. The PTT SD value should be **10 % or less**. A SD between 10 - 15% could be the result of physiological variation; a SD above 20% is not acceptable, in both instances, the measurement should be repeated.

PWV Quality Control

Warning Validation Error (#318)



The difference in Heart Rate between the two sites is too large. This could lead to an unreliable Pulse Wave Velocity result.

You should consider repeating the measurement.

HR difference = 12.4, [HR diff > 5].

OK

- A warning message will appear if the difference in heart rate between the capture sites is greater than 5 beats per minute
- The report will be generated with the heart rate difference noted with an asterisk
- The measurement should be repeated

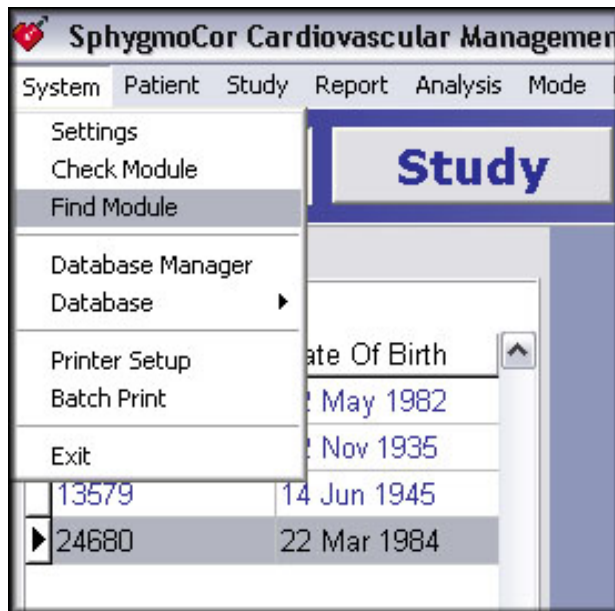
Site A-B	MeanT(ms)	SD(ms)	N	HR(bpm)
ECG-CAR	62.2	2.1	11	68
ECG-FEM	113.1	0.8	9	63*
CAR-FEM	50.9	2.2		

CAR-FEM PTT SD	4.4 %
Pulse Wave Velocity (m/s)	10.8 ± 0.5



Additional Software Features

Find Module



- 'Find Module' assists in detecting the SphygmoCor System communications port
- Accessed by clicking 'System,' then selecting 'Find Module'
- A pop-up box will appear confirming that the search is about to begin
- After searching all available COM ports, the software automatically selects the appropriate COM port
- Results will be displayed in bottom right of screen

SphygmoCor System – Exporting Data

The SphygmoCor System allows data to be exported in several formats:

- As a **graphic** (.jpg) file for use in MS *PowerPoint* or *Word* documents
 - Screenshot of any Report screen in PWA
 - Screenshot of the Report screen in PWV
- As a **text** (.txt) file for analysis in MS *Excel* documents
 - Entire database - every patient, every measurement
 - One single patient - every measurement
 - One individual measurement
 - Waveform and ECG data points also exported
- Exports are sent to C:\AtCor\SphygmoCor CvMS V9\Export folder (default setting); another pathway can be selected manually

SphygmoCor Database Management

- To avoid losing data, it is recommended that the SphygmoCor database be backed up on a regular basis

- To copy or create a back-up of the data:
 - Create a new folder on your PC in which to store database back-ups

 - Locate and copy the 'DATA' folder
 - Located within C:\AtCor\SphygmoCor CvMS V9 directory
 - Copy 'DATA' into the newly created back-up folder
 - Give the copy of 'DATA' a unique name with current date

 - To back-up exported data, copy 'EXPORT' folder as above
 - Located within C:\AtCor\SphygmoCor CvMS V9 directory

SphygmoCor Database Management

- To create an additional database:
 - From the patient tab, select System/Database Manager
 - Enter a name and description for the new database
 - Click the 'Create New' button, then click 'OK'
 - To select the new database, select 'System/Database Manager' from the patient tab. Select the desired database, then click 'Select' and then click 'OK'
 - The new database will be located within C:\AtCor\SphygmoCor CvMS V9 directory\data

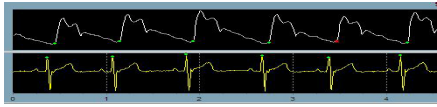


Review


The value of the SphygmoCor system:

- Non-invasive, quick assessment completed in an office setting
- Derives key information such as central pressures, the aortic pressure waveform and pulse wave velocity
- Easy to learn, easy to use
- Generates report with only ten seconds of data

SphygmoCor Protocol




**Augmentation Index,
Pulse Wave Velocity & Heart Rate
Variability**

Elaine Urbina, MD, MS
Director, Preventive Cardiology
Cincinnati Children's Hospital Medical Center 


Protocol Review: *Inclusion/Exclusion Criteria*

- **Inclusion criteria:**
 - Per CKiD
- **Exclusions:**
 - Pregnancy (for most studies)
 - Unable to lay supine
 - Significant arrhythmia
 - Are told to refrain from vasoactive drugs the AM of the test (tobacco, caffeine, decongestants, asthma medications).



Probable Visit Flow

- Anthropometrics
- BP - Prefer BP done with auscultatory technique (mercury or aneroid) within 1 hour of vascular testing but will accept up to 6 hours.
- Labs (fasting)
- Iohexol infusion
- Snack
- Echocardiogram
- Timed Blood Draw
- Lunch & Questionnaires
- Carotid Intima medial thickness (at select sites)
- Vascular tests ('SphygmoCor')
- Final Timed blood draw.
- ABPM



Order of Vascular Testing

- BP – 3 readings – *SITTING* with auscultatory technique (mercury or aneroid) within 6 hours of vascular testing.
- PWA – 3 readings – *SITTING* (time limit 15 minutes)
 - Calibrated to sitting BP, (supine BP is higher).
- PWV 3 readings (*carotid-femoral*) – *SUPINE* (time limit 15 minutes)
- HRV – 1 recording of exactly 10 minutes – *SUPINE* (at selected sites)
 - Must be resting (at least 5 minutes)
 - Try not to move patient as it causes artifact in ECG
 - Can't press on neck as pressure on carotid body changes autonomic function.




Open Excel SphygmoCor Worksheet

- This worksheet will calculate PWV distances and should be saved for future reference for all subjects.
- Must be opened prior to opening SphygmoCor software.
- Open “SphygmoCor Worksheet BLANK” in CKID folder on desktop.
- Save as new name using CKID & visit number:
Example: 283100v2.
- Then proceed with opening SphygmoCor software.



SphygmoCor: *Prepare the Device*

Connect the Type B Plug to the rear of the Electronics Module labelled 
Connect the Type A Plug to the computer, at USB port indicated by label.



Connect the Type B plug to the rear of the Electronics Module






Connect the Type A plug to the computer


- Appearance of device and cables may be different on older models.
- The device should be locked in a secure location after use.
- The room should be maintained at a normal ambient temperature.
- Use the USB Cable supplied with your system. It is a special cable that provides the power to the Electronics Module and the means for the computer to communicate with the Module.
- Connect the type B plug to the Electronics Module.
- Note the labels on your notebook computer and connect the type A plug to the specified USB port, failure to do so will result in an error and the computer will not recognize your module.



SphygmoCor: *Prepare the Device*






- Attach the ECG cable to the side of the module.
- Turn on the PC & the Standby/Ready indicator will be orange.
- Open the SphygmoCor software by double clicking the icon on the desktop.
- The Standby/Ready indicator will turn green (ready to take a measurement).
- If the module has any errors it will change to red.




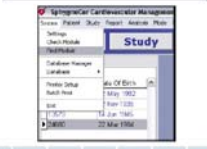
SphygmoCor: *Communication Errors*


- If a COMMUNICATIONS ERROR appears it is because either:
 - (a) The electronics module is not connected to the computer.
 - (b) The electronics module is not switched on.
 - (c) The selected computer communications port is incorrect.
- Click YES if you wish to try detecting the module again.
- If the module is not detected on its second attempt a message window will appear prompting you if you wish to change the configuration settings.
- If you click YES the SphygmoCor Configuration Window will appear, allowing you to change the computer communications port to which the electronics module is connected.
- If you only connect the device to the specified USB port on your laptop, you will avoid this problem.



SphygmoCor: *Communication Errors*

- You can also try to automatically find correct communication port.
- 'Find Module' assists in detecting the SphygmoCor System communications port
- Accessed by clicking 'System,' then selecting 'Find Module'
- pop-up box will appear confirming that the search is about to begin
- After searching all available COM ports, the software automatically selects the appropriate COM port
- Results will be displayed



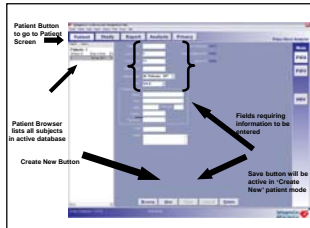
SphygmoCor: *Select Database*

- Click on System, then Database manager and a list of databases appears.
- Use the up/down arrows to scroll to and highlight the CKiDSTUDY database.
- Click on Select (lower left hand corner) and OK.



SphygmoCor: *Enter Subject Data*

- Click on NEW & enter **CKiD ID number**
- Enter **Site initials** for LAST name
- Enter visit number for FIRST name (i.e. most will be at **V2**; next vascular visit will be in 2 years)



- Leave DATE of BIRTH at **January 1, but change to 1960**. The software will not allow PWA on kids less than 18 years.
- Enter GENDER.
- Click SAVE and YES when it asks if you want to accept the changes.

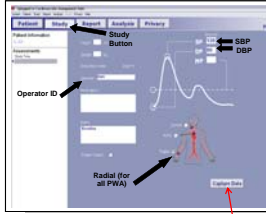
Augmentation Index



Protocol

Aix Protocol: *Select PWA*

- Click PWA along the right side of the screen.
- Click on STUDY (upper left).
- Enter the staff ID (your initials) in OPERATOR box.
- Be sure RADIAL is selected.
- Enter average SBP & DBP previously measured or use the worksheet to calculate if done immediately before the test.



Subgrouped Worksheet for CKiDs

CKiDs ID	Summary	Notes
001	001	001
002	002	002
003	003	003
004	004	004
005	005	005
006	006	006
007	007	007
008	008	008
009	009	009
010	010	010

- Save the worksheet in CKiDs folder (need to create this) on your laptop as CKiDsID_Visit#.xls (ie CKiDs999999_V2.xls)
- Click on CAPTURE DATA (bottom right) and the DATA CAPTURE SCREEN OPENS.

Aix Protocol: *Capture data*

- Pressure sensor is very small gray dot - precision of placement onto pulse is most critical factor for PWA
- When palpating the radial pulse, gently feel for the single location where the pulse amplitude is felt most strongly
- Once the pulse has been located with finger, slowly lift fingertip from pulse, looking for visual reference mark on the skin (hair, birthmark, vein)
- Keep your eye trained on this spot while moving tonometer next to wrist
- Visually connect the gray tip of the tonometer onto the reference mark you've located (roll the tonometer over top)
- Assume proper tonometry position

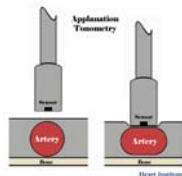


Tonometer Placement

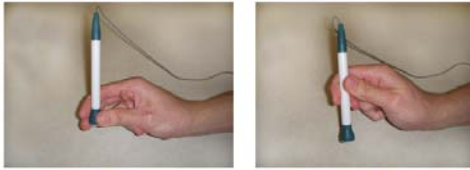


Aix Protocol: *Capture data*

- Place your index and middle fingers of the hand not holding the tonometer on the wrist near the base of the **RIGHT** thumb.
- Place the tonometer between the two fingers and press down gently.
- The best results are obtained if the wrist is bent outward (dorsiflex position).
- The **RIGHT** wrist should be supported by using a small cushion or the operator's hand.



Aix Protocol: *Capture data*



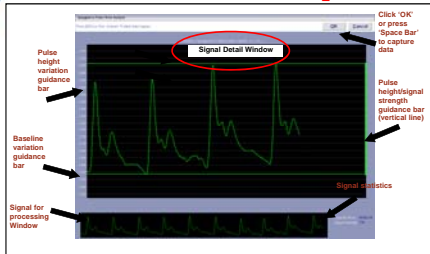
Correct Grip

Incorrect Grip

- The tonometer should be held at the base so that the operator's fingertips make contact with the patient's skin.
- Holding the tonometer higher on the shaft will allow less control and makes data capture more difficult.



Aix Protocol: *Capture data*



- The Signal Detail area is large area in the middle of the screen.
- The Signal Detail area is refreshed and re-scaled every 5 seconds.
- The software will auto scale and zoom to make the waveform large enough to fill the window.



Aix Protocol: *Capture data*



- The Signal for Processing area will display the entire waveform that will be processed.
- Make sure that you can see the BOTTOM AND TOP OF EACH WAVE IN THIS AREA and
- The WAVES CONSISTENTLY FILL THE WINDOW.



Aix Protocol: *Capture data*



- The Signal Statistics are on the bottom right.
- Capture time: is the time over which you have been capturing a signal.
- Signal Strength is the strength of the signal you are capturing

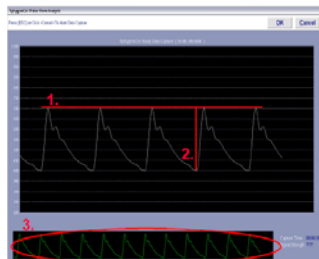


Aix Protocol: *Check Quality*

- Identify high quality PWA signal.
- Adjust the tonometer slightly backwards and forwards across the artery. As you move away from the center of the artery, the pulse waveform will become smaller. Once you have obtained a good waveform, you will notice that it is consistent, large and moving across the screen in a steady vertical position.
- If tracing is off the top or bottom of the screen, the operator is pressing too hard or not hard enough respectively. Look for a steady vertical waveform position



Aix Protocol: *Capture data*



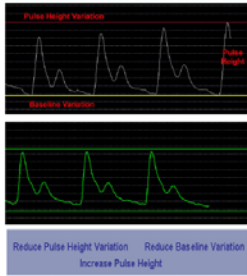
High quality data requires that the following conditions be satisfied:

1. Consistent Pulse Height
2. Large Waveform Amplitude (filling as much of the screen as possible)
3. Consistent waveform shapes for ten seconds

Note the lack of artifact and "noise" in the signal



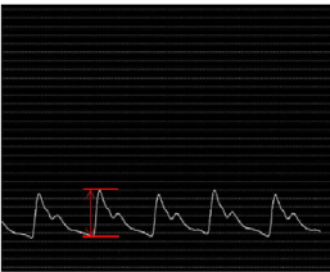
Aix Protocol: *Capture data*



- The bars are color-coordinated using red, yellow and green
- Pulse Height Variation & Baseline Variation
 - Red indicates a variation greater than 10%
 - Yellow indicates a variation between 5 – 10%
 - Green indicates a variation less than 5%
- Pulse Height:
 - Red indicates a height less than 75
 - Yellow indicates a height between 75 – 85
 - Green indicates a height greater than 85
- Messages regarding tonometer adjustment are also displayed at the bottom of the screen



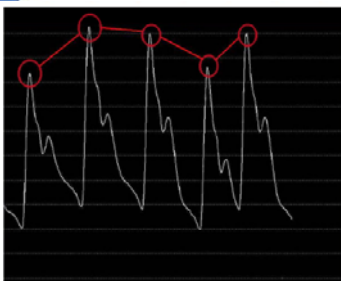
Aix Protocol: *Capture data*



- If the waveforms appear small:
- Wait until the signal scale is amplified as the signal reaches the right side of the screen
 - Press slightly harder to induce stronger signal
 - Adjust the tonometer positioning slightly so that the tip is over the strongest pulse point



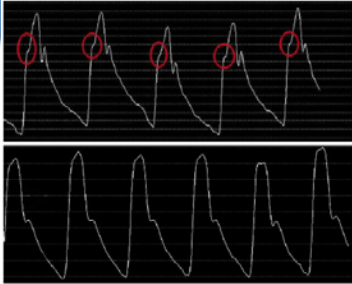
Aix Protocol: *Capture data*



- Pulse height inconsistency is most commonly caused by either inconsistent hold-down pressure or respiratory variation.
- Hold tonometer at the base with fingers touching the patient's skin
 - Ensure hand positioning is stable to maintain consistent hold-down pressure



Aix Protocol: *Capture data*



The initial upstroke of the waveform signal should be sharp from base to peak.

Improper tonometer positioning creates an inflection in the upstroke.

- Change the angle at which tonometer is held over the patient's pulse
- Adjust the location of the tonometer's tip



Aix Protocol: *Check Quality*

•**Look For:**

- Signal Strength should be NO LESS THAN 100. Usually 300 - 500.**
- Look for a steady vertical waveform position, with all pulses visible in signal for processing screen**
- A constant pulse height**
- Consistent waveform profiles for two complete screens (at least 10 seconds).**



Aix Protocol: *Capture Data*

- When in the Capture screen, If the horizontal lines going across and the vertical line on R turn green, then the tracing is good and the Autocapture mode will take the data to process. You may also press the spacebar or use the foot pedal to activate the capture request in any mode (PWA, PWV or HRV).**
- Remember, the last 2 seconds of displayed pulse waveform is discarded when data is captured. This allows the user up to two seconds between removing the tonometer from the artery and pressing the space bar or foot peddle.**
- After you have captured data successfully the REPORT Screen will appear.**
- Replace the tonometer in the tray immediately after capturing data (\$3000 to replace).**



Aix Protocol: *Detailed Screen*

DETAILED

121	114
68	69
88	88
53	45

- Device should go automatically to DETAILED screen.
- If not, click on DETAILED to get there.

Aix Protocol: *Generate Report*

REPORT

- Check the report for accuracy.
- If the patient data is incorrect, click the Patient tool-bar button (top left) to return to the patient screen and update patient details. Then click on report to return to report.
- If the study data is incorrect, click the MODIFY button. Change the incorrect details (i.e. wrong BP) in the Study Screen and click on MODIFY again.
- Check the Quality Control area. **GOOD READINGS ARE GREEN** There should be **NO NUMBERS IN RED**.

Aix Protocol: *Check Quality*

Top 4 numbers should be in GREEN!

- 1)Average Pulse Height: must be ≥ 80 (100 is even better).
- 2)Pulse Height Variation: should be $\leq 5\%$
- 3)Diastolic Variation: should be $\leq 5\%$. High value occurs with inconsistent pressure applied to the tonometer during the measurement.
- 4)Shape variation should be $\leq 4\%$.
- 5)Ignore Pulse Length Variation (it is related to HR)
- 6) Ignore Max dP/dt (diastolic P change over diastolic time change)

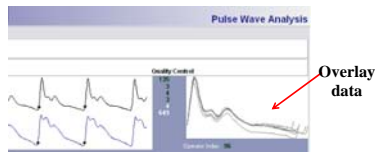
Aix Protocol: *Check Quality*



- Operator index: MUST be ≥ 80 . It is a 'weighted' value calculated from the other indices above.
 - Excellent = 95-100%
 - Good = 90- 94%
 - Acceptable = 85-90%
 - Borderline = 75-84%
 - Unacceptable = $\leq 74\%$



Aix Protocol: *Generate Report*



- Check to see that the overlay recorded data is visually coherent. That is, the waveform pulses should overlay with minimal spread.
- If values are outside of acceptable limits, delete the study by clicking on the DELETE button on the bottom of the REPORT Screen. When it asks if you are sure you want to delete the data, click YES. Then Click the STUDY Tool-bar button (or press F3) to return to the Study Screen.




Aix: *Time Considerations*

- If the study is taking too long, you may have to accept data with an Operator Index < 80 and reasonable wave form overlay, but with one of the QC numbers in red.
- Leave data missing if cannot reach these 'relaxed' QC guidelines:
 - 1) Average Pulse Height: Really must be ≥ 80
 - 2) Pulse Height Variation: between 5 - 10 %
 - 3) Diastolic Variation: between 5 - 10%.
 - 4) Shape variation between 4-8%.
 - 5) Ignore Pulse Length Variation
 - 6) Max dP/dt
- Record reason for missing measures in the protocol deviation log.
- No more than 3 readings per site should be saved.
- Keep best readings and delete additional readings by going to the report page and clicking on the Delete button.



AIx Protocol: *PWA Poor Waveforms*



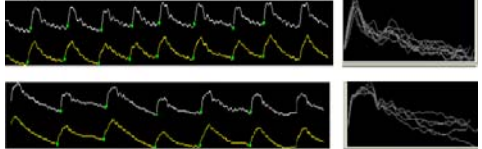
Bump in Ascending Radial Waveform

•The tonometer is not directly on top of the radial artery.

Cincinnati Children's
Heart Institute

AIx Protocol: *PWA Poor Waveforms*

Noisy signal



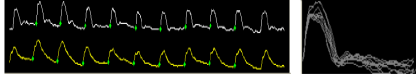
Vary in baseline

- The tonometer is not directly on top of the radial artery.
- Variation in the peaks/troughs = change in P applied, need to hold steady.
- May also be an unavoidable respiratory artifact.

Cincinnati Children's
Heart Institute

AIx Protocol: *PWA Poor Waveforms*

Flat Diastolic part



- Diastolic part of wave flat = hold-down P too high, artery is being occluded.

Cincinnati Children's
Heart Institute

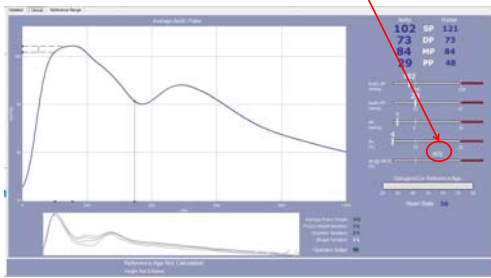
AIx Protocol: *AIx Not Calculated*



ACTION: Delete and Repeat



AIx Protocol: *AIx Not Calculated*

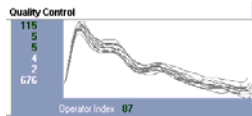


ACTION: Delete and Repeat



AIx Protocol: *NOTE warning*

- Ensure the report is **NOT** marked with the 'Note' flag
- Reports with '**Note:**' flag should be considered unacceptable (even if other QC parameters are adequate)



Repeat Modify Delete Export Print

Note:
Waveform Timing out of Range [Peripheral T1]



Pulse Wave Velocity

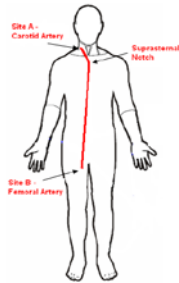


Protocol



PWV Protocol: *Measure Distance*

- Have the patient lie down in a comfortable position. Let them know they will be lying down for awhile.
- It is best to keep the head flat, not on a pillow. One may place a small roll under the neck if the patient is uncomfortable.
- Allow tape measure to rest lightly on body. Do not stretch 'as the crow flies.'
- Measure 3 times in cm and enter into SphygmoCor excel worksheet which will convert it to mm.



- Each measurement should differ by no more than 1 cm (i.e. 9.5, 8.9, 9.7 is ok but 8, 9.5, 10 is not, re-measure 3 more times)
- Record in CM in SphygmoCor worksheet, (1 cm = 10 mm).
- Worksheet converts to mm. **Device needs distance in MM.**



PWV Protocol:

Measure Femoral Distance

- Distal for FEMORAL: While supine, locate Femoral artery by placing fingers below inguinal ligament in groin (mark spot with water washable pen).
- Placing a roll under the hips helps to bring the artery to the surface



PWV Protocol:

Save Femoral Distance Measurement

- Measure distance from the SUPRA STERNAL NOTCH to the Femoral artery 3x using the tape measure.
- Hold ALT and press TAB to select previously opened SphygmoCor Excel Worksheet.
- Record values in the SphygmoCor Excel worksheet. Excel will calculate the DISTAL FEMORAL (or record on paper form and use calculator)

A = SSN to Femoral	Value	Total	AVG SSN to Femoral
Measure #	cm	all 3 values	Divide Total by 3
#1	0	0	0
#2	0		
#3	0		



PWV Protocol:

Measure Proximal (Carotid) Distance

- Proximal for all (Carotid to SSN): Find the strongest pulse at the PROXIMAL site (always carotid artery) by placing your index and middle fingers of the hand on the right side of the patient's neck up near jaw. Best to have patient's head flat (not on a pillow), or extended slightly backward by placing a roll under the shoulders (similar to positioning for an arch view for echo).
- Mark this spot with a washable marker.
- Place a mark in the center of the SUPRA STERNAL NOTCH.
- Measure from the CAROTID to SSN three times.
- Record values in the SphygmoCor Excel worksheet. Excel will calculate the PROXIMAL (Carotid) (or record on paper form and use calculator).
- RIGHT side is preferred. If L used, note reason in protocol deviation log.

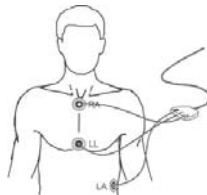


CAROTID to SSN (Proximal all)	Value	Total	AVG PROXIMAL
Measure #	cm	all 3 values	Divide Total by 3
#1	0	0	0.0
#2	0		
#3	0		



PWV Protocol: *Apply ECG Leads*

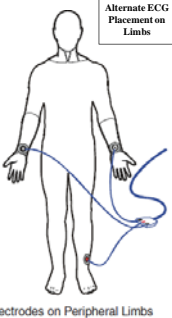
- Prepare the ECG site by using alcohol swabs to remove skin oils and creams.
- Use chest placement.
- WHITE ECG (RA) on top of sternum.
- BLACK ECG (LA) lead on the L side of abdomen.
- RED ECG (LL) on the bottom of sternum.
- **R WAVE SHOULD BE UPRIGHT.**



PWV Protocol: *Apply ECG Leads*

If males refuse to have chest shaved or lead placement on chest is not possible, may use modified chest leads:

- Place leads closer to the R & L shoulder and on the L side of the abdomen.
- Or try **LIMB LEADS**:
- Place the **WHITE ECG (RA)** on the **RIGHT ARM**.
- Place the **BLACK ECG (LA)** lead on the **LEFT**.
- Place the **RED ECG (LL)** on the **LEFT LEG**. Don't place over the radial artery where you need to palpate

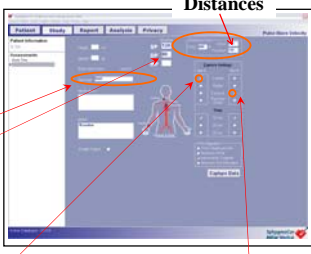


Electrodes on Peripheral Limbs

Cincinnati Children's Heart Institute

PWV Protocol: *Select PWV Distances*

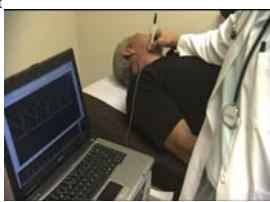
- Select PWV from the right of the screen.
- Click on **STUDY**. And patient screen appears.
- Enter the staff ID number in the **OPERATOR** box.
- Enter **SBP & DBP**.
- Enter **Distal distance** in mm (differs by distal type)
- Enter **Proximal distance** in mm (always same).
- Be sure site A set to Carotid.**
- Click on **Radial, Femoral or Distal** for arm, groin, foot for Site B.
- Leave the time 10 seconds for both sites (this is the capture time).
- Leave the PWV algorithm on **Intersecting tangents**.
- Click on **Capture data**.



Cincinnati Children's Heart Institute

PWV: *Capture Proximal (carotid)*

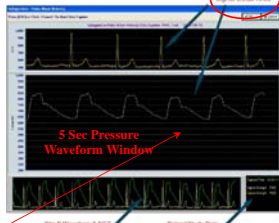
- Check ECG signal. If poor (irregular baseline or T waves that are as tall as the QRS):
 - re prep the skin or use abrasive ECG prep paste.
 - Change ECG leads (get dry).
- Place your index and middle fingers of the hand not holding the tonometer on the right side of the patient's neck over the previously placed mark.
- Place the tonometer between the two fingers & compress gently.
 - The best results are obtained if the head is flat on the bed and turned away slightly.
 - Use your fingers to prevent the artery from rolling.



Cincinnati Children's Heart Institute

PWV: Capture Proximal (carotid)

- Place your index and middle fingers of the hand not holding the tonometer on the right side of the patient's neck over the previously placed mark. Place the tonometer between the two fingers and compress it gently. The best results are obtained if the head is flat on the bed and turned away slightly. Use your fingers to prevent the artery from rolling.



- The Signal Detail area is the large area in the middle of the screen. The Signal Detail area is refreshed and re-scaled every five seconds. The software will auto scale and zoom to make the waveform large enough to fill the window. When the horizontal grid lines appear farther apart, the signal strength is better.



PWV: Capture Proximal (carotid)

- The Signal for Processing area will display the entire waveform & ECG that will be processed.
- Make sure that you can see the BOTTOM & TOP OF EACH WAVE IN THIS AREA and that the WAVES FILL THE WINDOW CONSISTENTLY.



- The Signal Statistics are on the bottom right
- Capture time: is the time over which you have been capturing a signal.
- Signal Strength is the strength of the signal you are capturing (both ECG & Pressure waves. This should be NO LESS THAN 100. Usually between 300 and 500 can be achieved.



PWV: Identify Quality Tracing

- If the tracing is off the top or bottom of the screen, the operator is pressing too hard or not hard enough respectively.
- Adjust the tonometer slightly backwards and forwards across the artery. As you move away from the center of the artery, the pulse waveform will become smaller.
- Once you have obtained a good waveform, you will notice that it is consistent, large and moving across the screen in a steady vertical position.
- Look for a steady vertical waveform position
- A constant pulse height
- Consistent waveform profiles for two complete screens (at least 10 seconds).



PWV Protocol: *Capture Data*

- When in the Capture screen, press the spacebar or use foot pedal to activate the capture request in any mode (PWA, PWV or HRV).
- Remember, the last 2 seconds of displayed pulse waveform is discarded when data is captured. This allows the user up to two seconds between removing the tonometer from the artery and pressing the space bar or foot peddle.



- A message box will pop up stating "Site A data captured successfully. Would you like to continue and capture site B data?"
- Click the YES button to proceed. The Data Capture Screen will appear again indicating readiness to capture DISTAL data.



Pulse Wave Velocity Technique

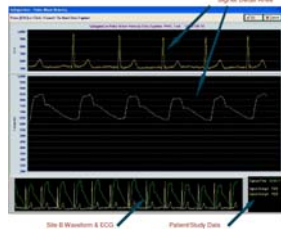
Tonometer Pressure and Positioning

- Do not be afraid to apply pressure with the tonometer (ask the patient to inform you if they become uncomfortable)
- Try different angles using response of the waveform on data capture screen to help you judge how to angle the probe
- Move the tonometer without picking it up (dragging the underlying skin while maintaining hold-down pressure)
- Make small adjustments: Left, right, proximal, distal. Wait 2 seconds to see how the waveform changes and determine how you should then make your next adjustment
- If you notice good, strong waveform that slowly begins to lose amplitude & strength likely due to artery rolling away: make slight adjustments to position/angle of tonometer to stabilize the artery. If you do not see an increase in waveform quality, pick up tonometer, re-palpate and place tonometer directly on top of artery



PWV: *Capture Distal (femoral, foot, radial)*

- Capture DISTAL data (FEMORAL).
- Place your index and middle fingers of the hand not holding the tonometer on the mark previously placed in the groin.
- Place tonometer between the 2 fingers and compress gently.



- Best results obtained if the leg is bent outward slightly.
- Identify quality data.
- Press spacebar or use foot pedal. The report screen will open.
- Replace the tonometer in the tray immediately after capturing data.



PWV: *Check for Quality*

•R wave on the ECG should be easily recognized. The device is using only the R waves with a green dot on them. Red dot ECG waves were rejected. Visually inspect to be certain the appropriate ECG spike is indicated by a green dot.



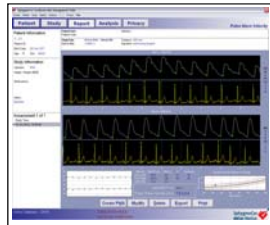
•It is important that the foot of the wave is easily identified. The device indicates good wave forms with a green dot and rejected waves with a red one. Visually inspect to be certain that only good waves are indicated with a green (not red) dot. Usually the green dot is slightly higher than the lowest part of the wave tracing.



PWV: *Check for Quality*

•The software requires a minimum of 3 pairs of data to calculate a result. For instance, you must have 3 ECG spikes matching up with 3 Pressure spikes.

•If it rejects too many pairs the software will not calculate a PWV.
•If you have been careful to make sure that the tracing does not go off the top or bottom of the screen this should not be an issue



PWV: *Check for Quality*



•The first two values (ECG-CAR and ECG-FEM) should be in **GREEN** not **RED** (ignore CAR-FEM). This means SD is $\leq 6\%$.



PWV: *Check for Quality*

Site A-B	MeanT(ms)	SD(ms)	N	HR(b/min)
ECG-CAR	62.2	2.1	11	78
ECG-FEM	113.1	0.8	9	79
CAR-FEM	50.9	2.2	3	

CAR-FEM PTT SD **4.4 %**

Pulse Wave Velocity (m/s) **10.8 ± 0.5**

- For Femoral, PTT SD should be **GREEN** (means PWV SD ≤ 10%).
- **Also NOTE:** Difference in HR between Proximal and Distal should be ≤ 5 BPM (may be hard in younger kids).
- If your final recording position is > 1 cm from your original mark: Re-measure 3 times and enter into spreadsheet to get average. Click on modify, enter new data, click on modify.

PWV Common Problems

Heart Rate

- Error 318 will appear if the difference between the carotid and femoral heart rate is greater than 5 beats per minute
- The report will still be generated and the heart rate difference will be noted with an asterisk
- Repeat the measurement if you have not spent too much time and delete the study with the large HR difference.
- Since children may have greater variation in HR, if unable to get HR difference <5 BPM, accept 2 best readings as long as all other QC measures are met.

Warning: Validation Error (#318)

The difference in Heart Rate between the two sites is too large. This could lead to an unreliable Pulse Wave Velocity result. You should consider repeating the measurement. HR difference = 8.7, [HR diff > 5].

Site A-B	MeanT(ms)	SD(ms)	N	HR(b/min)
ECG-CAR	111.0	2.2	11	81
ECG-FEM	199.4	3.8	13	89*
CAR-FEM	45.4	4.4		

CAR-FEM PTT SD 9.8 %

Pulse Wave Velocity (m/s) 11.7 ± 1.2

PWV: *Conclude the Study*

- If you are not doing HRV, exit SphygmoCor Software **FIRST**.
- Then turn off the PC.
- **TURN OFF PC PRIOR TO DEVICE.**
- Then disconnect cables if need to dis-assemble the device.

PWV: *Time Considerations*

- You may have to accept tracings that are less than ideal if it is taking a long time or subject cannot lay still any longer.
- Leave data missing if cannot reach these more 'relaxed' QC guidelines:
 - SD of the first two values (ECG-CAR and ECG-FEM) should be 6 -10% PTT SD should between 10 - 15%.
 - Difference in HR Proximal - Distal 5-10 BPM
- Record reason for missing measures in the protocol deviation log.
- No more than 3 readings per site should be saved.
- Delete additional studies by going to the report page and clicking on the Delete button.



Heart Rate Variability



Protocol



Theory of HRV



- Heart rate variability measures the time delay between sequential QRS complexes in the ECG.
- The SphygmoCor system uses these time delays to determine the normal-to-normal (NN) interval time.
- Once all of the intervals are obtained, the results can be analyzed in the
 - Time-domain: analysis with respect to time (statistical analyses including standard deviation – variability)
 - Frequency domain: analysis with respect to frequency of HR oscillations (changes).

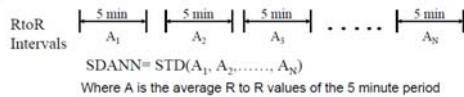


Time Domain HRV Measures

- **SDNN**: The standard deviation of all of the R-R, or Normal-to-Normal (NN) intervals is calculated.
- It reflects all the cyclic components responsible for variability in the period of the recording.
- It is an estimate of overall HRV
- A decreased SDNN has been associated with sudden cardiac death and is associated with LV dysfunction after acute MI.



Time Domain HRV Measures



- **SDANN** is the standard deviation of the average of the NN intervals calculated over short periods (5 minutes)
- It is an estimation of the changes in heart rate due to cycles longer than five minutes
- It reflects circadian rhythmicity of autonomic function.



Time Domain HRV Measures

- **PNN50** is the proportion of successive R -R Intervals with a difference greater than 50 msec.
- It is virtually independent of circadian rhythms.
- Reflects alterations in autonomic function that are primarily vagally (parasympathetic) mediated.

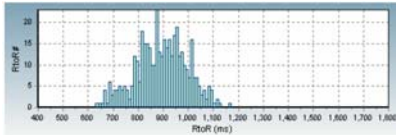


Time Domain HRV Measures

- **RMSSD**: The root mean squared successive difference is the square root of the mean squared differences of successive NN intervals
- RMSSD is an estimate of the short-term components of HRV
- It also reflects vagal tone.



Geometric HRV Measures



- **Triangular Index**= the integral of the density distribution divided by the maximum of the density distribution and given in msec
- It is an estimate of the overall HRV



Frequency Domain HRV Measures

- Also called 'Spectral Analysis' or 'Fast Fourier Analysis'
- Frequency of oscillations in HR are defined as:
 - Low Frequency = 0.04-0.15 Hz
 - influenced by both sympathetic and parasympathetic activity
 - High Frequency = 0.15-0.4 Hz
 - corresponds to parasympathetic activity
 - considered to be a marker of vagal activity
- The ratio of LF/HF represents the balance of parasympathetic and sympathetic activity



Frequency Domain HRV Measures

- More appropriate for short-term recordings (2-5 minutes)
- In patients surviving an acute MI, there was a reduction in total and individual power of spectral components
- In diabetic autonomic neuropathy you will find:
 - Reduced power in all spectral bands
 - Failure to increase LF on standing
 - Abnormally reduced total power with unchanged LF/HF
 - A leftward shift in the LF central frequency



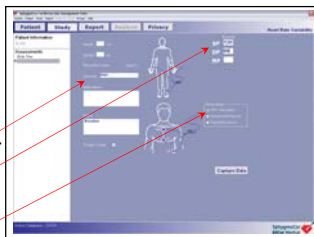
Types of HRV Measurements

- Resting
 - Time Domain
 - Frequency Domain
 - Geometric Measures
 - Poincaré plots
- Stress
 - Orthostatic (standing manoever)
 - Valsalva
 - Controlled breathing: since one of the main drivers of HRV is respiration.
- Most studies only collect data at rest.



HRV Protocol: *Select HRV*

- Select HRV from the right of the screen.
- Click on STUDY. And patient screen appears.
- Enter the staff ID number in the OPERATOR box.
- Enter SBP & DBP.
- Be sure HRV calculation is selected.



- Tell the subject to lay still as the test is about to begin.
- Press the capture button. During the capture, the blue ECG indicator labeled on the front panel will be illuminated.



HRV Protocol: *Start Session*



- You will see a horizontal trace of ECG in the **ECG Data Capture** Window. Ensure that a quality ECG trace is seen but the beat to beat R to R intervals chart is not yet activated. Check ECG signal.
- If poor (irregular baseline or T waves that are as tall as the QRS):
 - re prep the skin or use abrasive ECG prep paste.
 - Change ECG leads (get dry).



HRV Protocol: *Start Session*

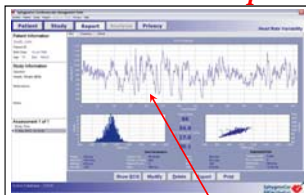


- When you are satisfied with the quality of the signals, start recording by pressing the **Start Session** button on the top right of the screen.
- The **beat to beat R to R intervals chart** will now be activated and updated every 5 seconds.
- Make sure the patient does not talk or move.
- Values relating to Elapsed Time, Number of Pulses, Average R to R Interval and Average Heart Rate will also be updated every 5 seconds.



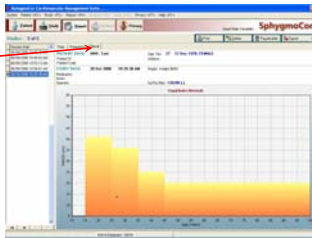
HRV Protocol: *Generate Report*

- After 10 minutes of good quality data (will accept no <9 or >11 min), press the **Calculate** button in the top right of the capture screen or press the Footswitch.
- The HRV Report Screen will be displayed.
- Examine the report for quality: The plot shows beat to beat R to R intervals of the whole recording. An interval marked with a red star indicates that it had been rejected and it will not be used in the HRV calculation. An interval will be rejected when it is uncharacteristically too high or too low compared to previous intervals.
- Ectopic beats are automatically discarded from the ECG. Ectopic beats are defined as significant changes to the R-to-R intervals from the previous beat. As long as the number of ectopic beats is <35% of the total number of beats, the HRV calculation will be deemed acceptable.



HRV Protocol: *Check Quality*

- Click on CLINICAL Tab.
- Look for inconclusive label (this will also be displayed under the 'Time' tab)
- "Inconclusive" means one of the following parameters is too large.
- The report should be discarded and measurement repeated.

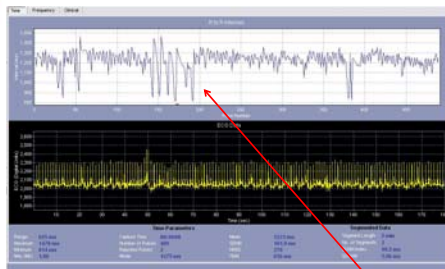


• Items judged:

- Percentage of rejected pulses (pulses with very high or very low R to R values) compared to accepted pulses
- RMS SD (should be < 250)
- PNN50 (should be < 70)
- R wave should be upright.



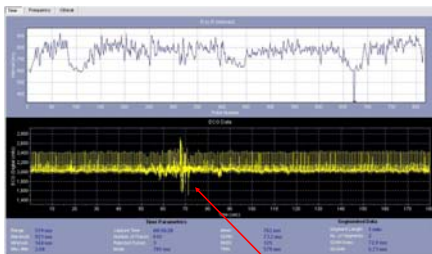
Protocol Review: *Poor Quality Studies*



- Examine 'Tachogram' for any unusual spikes (either up or down).
- This tracing should be repeated.



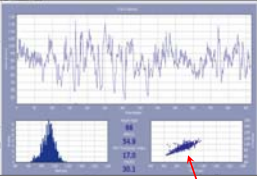
Protocol Review: *Poor Quality Studies*



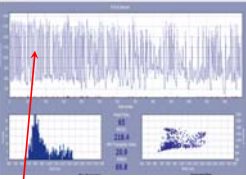
- Examine raw ECG for any unusual spikes (either up or down).
- This tracing should be repeated.



HRV Protocol: *Artifact*




GOOD




ARTIFACT


- Examine the report for quality: Very large narrow spikes may be artifact.
- Poincaré plot should look like a comet.



Data Management




Protocol




Certification – *Create Database*

- New staff will perform 3 resting PWA, PWV (carotid-femoral,) and 3 HRV measure on 3 volunteers (a repeat 'QC' visit may be requested if there are any concerns about reproducibility).
- Data will be sent to Vascular center who will notify coordinating center of successful certification
- First, create a database called TRAINING (vs CKIDSTUDY database) to keep data separate.

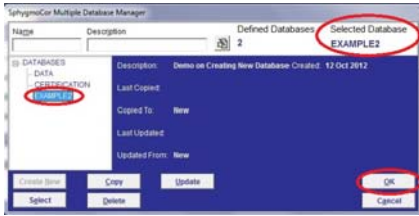


- Launch the SpymoCor software and click on 'System' located in the upper left-hand corner of the toolbar. In the drop-down menu, click on 'Database Manager.'
- Once the SpymoCor Multiple Database Manager window opens, enter a Name (Training or CKIDs) & Description for the database being created.
- Then click on 'Create New' in the lower left hand corner



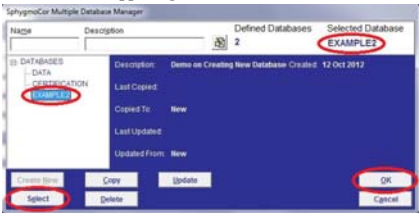
Creating a Database

- The newly created database will now appear in the list of databases and will automatically be the selected database. Clicking on 'OK' will open the newly created, blank database



Opening a Database

- When the SphygmoCor software is launched, the default database is opened. To access another database (Training or CKIDSTUDY), click on 'System' located in the upper left-hand corner of the toolbar. In the drop-down menu, click on 'Database Manager' and SphygmoCor Multiple Database Manager will open.
- Highlight desired database by clicking on database name, then click 'Select'; ensure the desired database is listed under 'Selected Database' in the upper right-hand corner, and then click 'OK.'



Certification Procedures

CKIDs Vascular Certification Log

Staff ID		PWA				
Subject	Volunteer ID No.	Measure No.	Date	Time	Notes (any problems or protocol deviations)	
1		1				
		2				
		3				
		1				

- Perform 3 resting PWA, PWV (carotid-femoral) and 3 HRV measure on 3 volunteers. A repeat 'QC' visit may be requested if there are any concerns about reproducibility.
- Create TRAINING database (don't use CKIDSTUDY database) to keep the data separate.
- Assign any ID number you choose (Staff ID number if a staff member).
- Fill out the Certification log, download data and send data & log to Vascular center for calculation of variability.
- Vascular center will notify Coordinating Center of successful certification.
- For ongoing QC, operator at each site must submit at least one PWV, one PWA, and one HRV study ideally, every 3 months (but no longer than 6 months). If there are no CKID participants scheduled, submit a complete (PWA, PWV, HRV) study on a single volunteer.



Protocol Deviation Log

CKIDs Vascular Protocol Deviation Log						
ID#	Date	Measure Time	Measure Type	Staff ID (Initials)	Protocol Deviation	Needs Physician Review: Y or N
XXXX	1/18/2008	8:53:00	PWA	JED	Only got 2 PWA in over 1 hour	N
XXXX	1/22/2008	10:00	PWV	SRO	Only got 1 PWV due to severe ACHO	N
XXXX	1/18/2008	12:21:00, 12:52:00	HRV	HRM	HRV may have artifact	Y
XXXX	1/21/2008	12:14	PM	STR	Movement artifact, delete 2nd of 4 measures based	N

- Record Protocol deviations in the protocol deviation log in Excel. Send to coordinating center with every data download.
- Examples of deviations to record:
 - Temp of room very high/low
 - Can't get readings (won't stay still, injury to limb, arrhythmia)
- Unusually high fat or carb diet
- Use of vasoactive drugs am of test (caffeine, tobacco, decongestants, asthma medications).

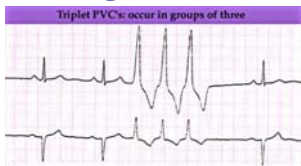


Flag Procedures

- A 'flag procedure' is the protocol used to notify the Principal investigator of an abnormal study.
- Each site will report the 'flagged' procedure to their study site PI & to the coordinating center.
- Typical reasons for flagging a study:
 - Very high BP
 - Very fast or slow HR
 - Very irregular HR
 - Abnormal beats (arrhythmia)
- Urgent reasons to flag a study are:
 - HR > 150 or < 50
 - Irregular HR associated with dizziness, shortness of breath, chest pain or other symptoms
 - Any study that makes you feel 'uncomfortable'



Flag Procedures



- Once a study is flagged, decide if it is 'urgent' or 'routine'
- If 'urgent', contact your PI and coordinating center by phone
- If 'routine', download a 'screen shot' as a .jpeg and email with a description of what you suspect is abnormal to the PI and the coordinating center (CoC)
- CoC will decide if additional testing or referral needed
- CoC will contact the research assistant to let them know if they need to delete the reading.



Downloading Screen Shots



- Turn on your device and laptop and open SphygmoCor program.
- Open database where questionable study is located.
- Open patient with questionable study
- Click on type of study (PWA, PWV, HRV)
- Click on the time the questionable reading was performed.
- Click on report

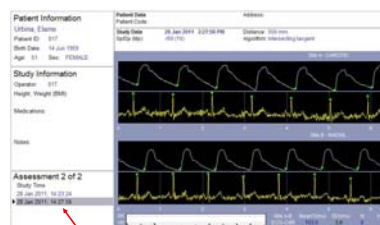


Downloading Screen Shots

- Click on Export , SphygmoCor Export window will be displayed.
- Click on SELECT & then desktop. Open the SEARCH export file folder by double clicking on it.
- Click on Open to close this window.
- Click on export (bottom left) and the study will be exported as a picture (*.jpeg)
- Click on close.
- Go to desktop, open search export folder and copy file to thumb drive to email on internet-ready computer.
- Email questionable screen shots and a description of what you suspect is abnormal to the CoC.
- CoC will let you know if it should be deleted.



Deleting Poor Quality Studies

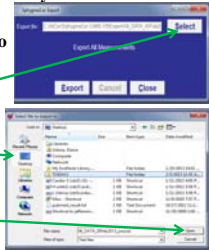


- Open the SphygmoCor program and select the appropriate database.
- Click on the patient of interest to highlight it. Select PWA, PWV, HRV.
- Click on REPORT
- Find the study to be deleted from the STUDY TIME list on the left hand column and click once to highlight it.
- Click the DELETE button on bottom to delete. You will get a message 'This will delete the Measurement for patient LAST, FIRST are you sure? Click Yes.



PWA, PWV, HRV: *Export Study*

- Export on first screening day of every calendar month or after each new set of measurements, whichever is less frequent (If you download on May 1 and don't see another patient until June 15, download on June 15, not June 1).
- From the Patient window, Select PWA (or PWV or HRV). Need to export each 'type' of test separately.
- Click on System (top left corner) and then Database and scroll to the right to click on Export as text.
- The SphygmoCor Export window opens.
- Click on SELECT
- Click on desktop.
- Click on CKiD folder (created previously).
- Click on Open.



PWA, PWV, HRV: *Export Study*

- Add your site abbreviation to the beginning of the file name supplied by the device & click Open. The export will now go to CKiD folder.
- Click on export. When 'successfully exported xx of xx records' message appears, click close.
- Repeat for PWV & HRV.
- Close the program.
- Locate & open CKiD folder on desktop
- Find the files (PWA, PWV, HRV) and copy to encrypted thumb drive.
- Transfer to secure location (either on your PC or hospital network).
- CoC will request approximately every 6 months. Email to CKIDPWV@email.chop.edu.



Export to SCOR file

- Export studies to SCOR file once a month
- File includes all PWA, PWV, HRV
- Can only be re-imported into SphygmoCor software (cannot be read by other programs)



CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

**SECTION 34: VASCULAR TESTS DATA TRANSMISSION
AND SUBMISSION**

34.1 VASCULAR TESTS COORDINATING CENTER HANDLING OF DATA

A separate .txt file export from the “CKIDSTUDY” database in SphygmoCor will be created for Pulse Wave Analysis (PWA), Pulse Wave Velocity (PWV), and Heart Rate Variability (HRV) (if applicable) containing all CKiD measurements to date and sent to CKIDPWV@email.chop.edu at the Vascular Tests Coordinating Center (VTCC) every 3 months (but no longer than 6 months). If no CKiD Vascular Tests have been performed since the last data export, the site should submit a group of Vascular Tests (PWA, PWV, HRV) performed on a healthy control; de-identified Vascular Tests collected clinically or for another research study will also be accepted (see your local site IRB regulations). Upon receipt of the .txt file data exports, the VTCC will perform the following actions:

1. Email confirmation of receipt to the clinical site.
2. Import the .txt file into an appropriate data manipulating program. Txt files will be archived on shared server at VTCC and backed-up on a regular basis to an external database kept in a secure location.
3. Remove studies previously received at time of prior data export (each data export is cumulative from the beginning of the study), retaining only “new” studies.
4. Check submitted studies for pre-determined Quality Control (QC) indices built into the SphygmoCor program (see MOP Section 33.12).
 - a. If QC indices not met, the clinical site will be given a summary of the discrepancies.
 - b. Two consecutive deficient studies without documented extenuating circumstances (i.e., patient unable to sit still) will trigger recertification.
 - c. Sites should assume if not contacted that submitted studies were compliant.
5. Studies will be transferred to cumulative “clean” dataset (also saved to secure server and archived to external device regularly), which will be sent to the Data Coordinating Center (DCC) on a monthly basis.

34.2 DATA FORMAT AND DELIVERY

Data will be delivered to the DCC (KIDMAC) in cumulative “clean” excel files (also saved to secure server and archived to external device regularly). However, KIDMAC has the ability to receive the data in other formats, such as ASCII files. The file or group of files will be emailed to the DCC on a monthly basis. Upon arrival at KIDMAC, KIDMAC will send a confirmation email to the VTCC.

Appendices A - C list the variable names contained in the database for each of the tests, PWA (Appendix A), PWV (Appendix B) and HRV (Appendix C).

PWA exported fields.

Below is a list of the fields that are exported when a complete PWA database export is performed:

System ID	System Serial Identification Number
Database ID	Database Identification
Patient Number	Patient Number
Surname	Entered Patient's Surname
First Name	Entered Patient's First Name
Sex	Entered Patient's Sex
Date Of Birth	Entered Patient's Date of Birth
Patient ID	Entered Patient's Identification
Patient Code	Entered Patient Code
Patient Notes	Entered Patient Notes
SP	Entered Systolic Pressure
DP	Entered Diastolic Pressure
MP	Entered Mean Pressure
DATA_REV	Math's Data Revision
DATETIME	Date & Time of Study
AGE	Patient Age on Date of measurement
MEDICATION	Entered Medication
NOTES	Entered Notes
OPERATOR	Entered Operator
INTERPRETATION	Entered Interpretation
HEIGHT	Entered Height
WEIGHT	Entered Weight
BODY_MASS_INDEX	Body Mass Index
SAMPLE_RATE	Raw Data Sample Rate
SIMULATION_MODE	Simulated Report (Yes/No)
Tonometer Serial Number	Entered Tonometer Serial Number
SUB_TYPE	Entered Artery
Inconclusive	Inconclusive Report (Yes/No)
PPAmpRatio	Pulse Pressure Amplification Ratio Radial/Central
P_MAX_DPDT	Peripheral Pulse Maximum dP/dt
ED	Ejection Duration (ms)
CalcED	Calculated Ejection Duration (ms)
QUALITY_ED	Confidence Level of ED (3-Very Weak/2-Weak/1-Strong/0-Very Strong)
P_QC_PH	Peripheral Pulse Quality Control Pulse Height
P_QC_PHV	Peripheral Pulse Quality Control Pulse Height Variation
P_QC_PLV	Peripheral Pulse Quality Control Pulse Length Variation
P_QC_DV	Peripheral Pulse Quality Control Diastolic Variation
P_QC_SDEV	Peripheral Pulse Quality Control Shape Deviation
Operator Index	Calculated Operator Index
P_SP	Peripheral Systolic Pressure
P_DP	Peripheral Diastolic Pressure
P_MEANP	Peripheral Mean Pressure
P_T1	Adjusted Peripheral T ₁
P_T2	Adjusted Peripheral T ₂
P_AI	Peripheral Augmentation Index
P_CalcT1	Calculated Peripheral T ₁
P_CalcT2	Calculated Peripheral T ₂

P_ESP	End Systolic Pressure
P_P1	Peripheral P ₁
P_P2	Peripheral P ₂
P_T1ED	Peripheral T1/ED %
P_T2ED	Peripheral T2/ED %
P_QUALITY_T1	Peripheral Confidence Level of T1 (3-Very Weak/2-Weak/1-Strong/0-Very Strong)
P_QUALITY_T2	Peripheral Confidence Level of T2 (3-Very Weak/2-Weak/1-Strong/0-Very Strong)
C_AP	Central Augmented Pressure
C_AP_HR75	Heart Rate Corrected Central Augmented Pressure
C_MPS	Central Mean Pressure of Systole
C_MPD	Central Mean Pressure of Diastole
C_TTI	Central Tension Time Index
C_DTI	Central Diastolic Time Index
C_SVI	Central Buckberg Sub-Endocardial Viability Ratio (SEVR)
C_AL	Augmentation Load
C_ATI	Augmentation Time Index
HR	Heart Rate
C_PERIOD	Central Pulse Period
C_DD	Central Diastolic Duration
C_ED_PERIOD	Central ED/Period %
C_DD_PERIOD	Period-ED/Period %
C_PH	Central Pulse Height
C_AGPH	Central Aug/PH %
C_AGPH_HR75	Heart Rate Corrected Central Aug/PH %
C_P1_HEIGHT	Central Pressure at T1 - Dp
C_T1R	Time of the Start of the Reflected Wave
C_SP	Central Systolic Pressure
C_DP	Central Diastolic Pressure
C_MEANP	Central Mean Pressure
C_T1	Adjusted Central T1
C_T2	Adjusted Central T2
C_AI	Central Augmentation Index
C_CalcT1	Calculated Central T ₁
C_CalcT2	Calculated Central T ₂
C_ESP	Central End Systolic Pressure
C_P1	Central Pressure at T1
C_P2	Central Pressure at T2
C_T1ED	Central T1/ED %
C_T2ED	Central T2/ED %
C_QUALITY_T1	Central Confidence Level of T1 (3-Very Weak/2-Weak/1-Strong/0-Very Strong)
C_QUALITY_T2	Central Confidence Level of T2 (3-Very Weak/2-Weak/1-Strong/0-Very Strong)

PWV Exported Fields

Below is a list of the fields that are exported when a complete database export is performed:

System ID	System Serial Identification Number	PP_DEVIATION	Pulse to Pulse Deviation
Database ID	Database Identification	PWV	Pulse Wave Velocity
Patient Number	Patient Number	PWVERR	Pulse Wave Velocity Error
Surname	Entered Patient's Surname	PTT_SD	Pulse Transit Time Standard Deviation
First Name	Entered Patient's First Name	Tonometer Serial Number	Entered Tonometer Serial Number
Sex	Entered Patient's Sex	A_SUBTYPE	Site A Artery Location
Date Of Birth	Entered Patient's Date of Birth	A_NOF_10_SETS	Site A No of 10sec data sets
Patient ID	Entered Patient' Identification	A_HR	Site A Heart Rate
Patient Code	Entered Patient Code	A_MDT	Site A Mean Δt
Patient Notes	Entered Patient Notes	A_DEVIATION_DT	Site A Deviation
SP	Entered Systolic Pressure	A_TON_QC_PH	Site A Pressure Pulse Height
DP	Entered Diastolic Pressure	A_TON_QC_PHV	Site A Pressure Pulse Height Variation
MP	Entered Mean Pressure	A_TON_QC_PLV	Site A Pressure Pulse Length Variation
DATA_REV	Math's Data Revision	A_TON_QC_BLV	Site A Pressure Base Line Variation
DATETIME	Date & Time of Study	A_ECG_QC_PH	Site A ECG Pulse Height
AGE	Patient's Age on Date of Study	A_ECG_QC_PHV	Site A ECG Pulse Height Variation
MEDICATION	Entered Medication	A_ECG_QC_PLV	Site A ECG Pulse Length Variation
NOTES	Entered Notes	A_ECG_QC_BLV	Site A ECG Base Line Variation
OPERATOR	Entered Operator	B_SUBTYPE	Site B Artery Location
INTERPRETATION	Interpretation	B_NOF_10_SETS	Site B No Of 10 Sec Data Sets
HEIGHT	Entered Height	B_HR	Site B Heart Rate
WEIGHT	Entered Weight	B_MDT	Site B Mean Δt
BODY_MASS_INDEX	Body Mass Index	B_DEVIATION_DT	Site B Deviation
SAMPLE_RATE	Raw Data Sample Rate	B_TON_QC_PH	Site B Pressure Pulse Height
SIMULATION_MODE	Simulated Report (Yes/No)	B_TON_QC_PHV	Site B Pressure Pulse Height Variation
PX_DIST	Proximal Distance	B_TON_QC_PLV	Site B Pressure Pulse Length Variation
DT_DIST	Distal Distance	B_TON_QC_BLV	Site B Pressure Base Line Variation
PWV_DIST	PWV Distance	B_ECG_QC_PH	Site B ECG Pulse Height
PWV_DISTERR	PWV Distance Error	B_ECG_QC_PLV	Site B ECG Pulse Length Variation
ALGORITHM	Pressure Waveform Algorithm Selected	B_ECG_QC_BLV	Site B ECG Base Line Variation
PHEIGHT_PC	Pulse Height Algorithm - Percentage PH		
PP_MDT	Pulse to Pulse Mean Δt		

HRV Exported Fields

Below is a list of the fields that are exported when a complete database export is performed:

System ID	System Serial Identification Number
Database ID	Database Identification
Patient Number	Patient Number
Surname	Entered Patient's Surname
First Name	Entered Patient's First Name
Sex	Entered Patient's Sex
Date Of Birth	Entered Patient's Date of Birth
Patient ID	Entered Patient' Identification
Patient Code	Entered Patient Code
Patient Notes	Entered Patient Notes
SP	Entered Systolic Pressure
DP	Entered Diastolic Pressure
MP	Entered Mean Pressure
DATA_REV	Math's Data Revision
DATE TIME	End Date & Time of Study
AGE	Patient's Age on Date of Study
MEDICATION	Entered Medication
NOTES	Entered Notes
OPERATOR	Entered Operator
INTERPRETATION	Entered Interpretation
HEIGHT	Entered Height
WEIGHT	Entered Weight
BODY_MASS_INDEX	Body Mass Index
SAMPLE_RATE	Raw Data Sample Rate
SIMULATION	Simulated Report (Yes/No)
START_TIME	Start Date & Time of Study
METHOD	Study Mode
NUMBER_PULSES	Number of Captured Pulses
START_PULSE	Index of the First Pulse
END_PULSE	Index of the Last Pulse
MEAN	Mean R to R Interval
MAXIMUM	Maximum R to R Interval
MINIMUM	Minimum R to R Interval
MAX/MIN	Ratio of Maximum to Minimum R to R Interval
RANGE	Difference between the Maximum and Minimum R to R Intervals
SDNN	Standard Deviation of R to R Intervals
MODE	The most frequent R to R Interval
NN50	Number of consecutive R to R Intervals differing by more than 50ms
PNN50	Percentage of consecutive R to R Intervals differing by more than 50ms

RMSSD	Root Mean Square of the Difference of Successive R to R Intervals
HRV_TRIANGULAR_IND	Number of Pulses Divided by the Maximum Height of the Histogram
TINN	The Width of the Histogram
SEGMENT_LENGTH	Segment Length in Minutes (default 5 minutes)
NUMBER_SEGMENTS	Number of Segments
SDANN	Standard Deviation of the Means for each R to R Segment
SDNN Index	Mean of the Standard Deviations for each R to R Segment
STAND_HIGH	Highest Heart Rate Between the 5th and 25th Pulse During a Stand Manoeuvre
STAND_LOW	Lowest Heart Rate Between the 21 st and 45 th Pulse During a Stand Manoeuvre
STAND_RATIO	Ratio of Stand High to Stand Low
VALSALVA_HIGH	Highest Heart Rate During a Valsalva Manoeuvre
VALSALVA_LOW	Lowest Heart Rate Proceeding Valsalva High During a Valsalva Manoeuvre
VALSALVA_RATIO	Ratio of Valsalva High to Valsalva Low
SPECTRUM_POINTS	Number of Frequency Spectrum Points (default 128)
LF_POWER	Power in Low Frequency Range (0.04 – 0.15Hz)
LF_POWER_NORMALIS	Percentage of Low Frequency Power in the Low to High Frequency Range (0.04 – 0.4Hz)
HF_POWER	Power in High Frequency Range (0.15 – 0.4Hz)
HF_POWER_NORMALIS	Percentage of High Frequency Power in the Low to High Frequency Range (0.04 – 0.4Hz)
LF_HF_RATIO	Ratio of Low Frequency Power to High Frequency Power
LF_MAXIMUM	Frequency of Maximum Power in the Low Frequency Range
HF_MAXIMUM	Frequency of Maximum Power in the High Frequency Range
SPECTRUM_MAXIMUM	Maximum Power in the Low to High Frequency Range
TOTAL_POWER	Total Power in the Power Spectrum

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SECTION 35: HEALTH LITERACY ASSESSMENT

35.1 INTRODUCTION

This section describes how to administer the Health Literacy Assessment (HLA). The HLA is to be administered to parents or legal guardians of all individuals enrolled in CKiD, as well as by CKiD participants who are 15 years of age or older. The HLA is based on the Short Test of Functional Health Literacy Assessment (STOFHLA), which is a standardized tool. The HLA consists of two STOFHLA components: 1) numeracy and 2) reading comprehension. Brief descriptions of the two components are provided below. Because of the standardized nature of this assessment, all questions must be administered as they are written, and cannot be edited or rephrased.

35.1.1 Numeracy Assessment Overview

The numeracy assessment consists of a series of four (4) questions that assess the respondent's ability to read and understand numbers. The questions are based on Prompt Cards shown to the respondent. Each prompt contains instructions or basic information that one may be given in a healthcare setting. Each prompt has a corresponding question. The respondent will use the information on the card to answer the question that will be read to them by the administrator. The respondent has four (4) minutes to complete the assessment.

35.1.2 Reading Comprehension Assessment Overview

The reading comprehension assessment contains 36 reading comprehension items in two (2) passages. These passages test understanding of health care texts such as preparation for a diagnostic procedure and Medicare Rights and Responsibilities. The respondent is asked to select a correct response from a list of four possible choices and has seven (7) minutes to complete the assessment.

35.2 MATERIALS NEEDED

To perform the Health Numeracy and Reading Comprehension Assessments, the following items are needed:

- Stopwatch
- Laminated Prompt Cards (provided by CCC)
 - 4 numeracy test cards (Prompt 1 – 4)
 - 1 reading comprehension example card (Section C example)
- HLA01a form (for a parent/guardian only) – only one parent/guardian needs to complete the assessment
- HLA01b form (for CKiD participants \geq 15 years only)
- HLA01 Cheat Sheet
- Two pens

35.3 SPECIAL CONSIDERATIONS

35.3.1 Testing Low Literate Patients

An important part of health literacy features personal ability. Those with few or reduced skills often feel vulnerable when literacy inability is brought to their attention or to the attention of those around them. The force of this vulnerability is heightened by peer and social pressure. Consequently, low literate persons employ sophisticated mechanisms to conceal their literacy skill level and to prevent subsequent discovery or embarrassment, not to mention outright anger.

You very likely will encounter some of these low literacy behaviors:

- Pointing to the text with a finger, while reading
- Lifting the text closer to be read
- Claiming “the light’s not good”
- Complaining about “having trouble seeing”
- Expressing fatigue
- Explaining that they don’t have time
- Stating that they don’t think the material is interesting

When you encounter low literacy, soften the impact of unmasking by stating compassionately, **“I am not here to embarrass you, frustrate you, or make you feel uncomfortable. I am willing to stop if you want to, but the information you can give me is very special and valued highly by all of us here. (PAUSE) May I continue?”** Honor the dignity to which every human is entitled.

35.3.2 Visual Acuity

Routinely, low literate persons will mask reading problems by saying that they cannot see the materials they are given. This test is printed in 14 point font (large print) appropriate for persons with visual acuity of at least 20/50. If the respondent wears glasses, ask them to put them on for this test.

35.3.3 Language Preference

If the patient’s dominant language is Spanish, please do not administer the English version of the HLA01 form. Spanish speaking participants should be administered the Spanish version of the HLA01 form.

35.4 INSTRUCTIONS FOR COMPLETING THE ASSESSMENTS

The following instructions can also be found on the HLA01 Cheat Sheet. These instructions should be used in conjunction with the HLA01a and HLA01b form. The HLA01a form should be used for parents/guardians, and the HLA01b form should be used for CKiD participants who are 15 years of age or older.

35.4.1 Section A: General Information

Read the following script verbatim to the test respondent:

“Thank you for participating in this study. Please listen to each question carefully. As with all study information, your answers will be kept private. No one will know who completed this assessment, because there is only a code number at the top, not your name. Please answer all questions honestly. Your answers are for research purposes only.”

35.4.2 Section B: Numeracy Assessment Instructions

****The numeracy assessment will be timed for 4 minutes and is interview-assisted.****

There are four (4) numeracy Prompt Cards. Each prompt contains information or directions that may be given in a healthcare setting. Each prompt has a corresponding question. The questions are found on the HLA01 form. After the respondent has read the prompt card, you will read each question to the respondent and they will use the information on the card to answer the question. You will record their answer on the appropriate HLA01 form.

Please follow the steps below to administer this test:

1. Hand respondent Prompt 1 and read the following script:
“One of our most important goals as health care providers is to make sure we take time to explain instructions about your care in a way that is clear and will not cause any confusion. Today you can help us measure how well we are doing our job, by going through this exercise.

Do you wear glasses? (IF YES...) Please put them on.

This card contains directions you may be given in a healthcare setting. Please read the information in the box and use it to answer the question that I will read to you. If you do not know the answer, please say ‘I don’t know’. I will be handing you a total of four (4) cards which you will read to yourself, and then I will ask you one question about the information you just read. You will have 4 minutes to answer all 4 questions.”
2. Instruct the respondent to read the information in the prompt box; tell them to say “Done” or “Finished” when they have finished reading.

***Remember to start the stopwatch when the respondent begins reading Prompt 1. Stop the timer after 4 minutes and remove the prompt cards from the respondent, even if they have not finished answering all questions.**

3. When the respondent indicates that they have finished reading the contents of the box, read the question for the prompt to the respondent. Record their answer verbatim in the space provided on the appropriate HLA01 form.
4. Hand the respondent the next prompt to read. Repeat steps 2 and 3 above. Do this until the question for the last prompt (Prompt 4) has been answered or when 4 minutes have elapsed, whichever occurs first.

35.4.2.1 Special Directions for Uniform Administration

Prompt 1: Be sure you read 7:00 a.m. and not “in the morning.” Part of the test intention for this prompt is to determine if the patient understands that “a.m.” means morning”. Remind the respondent to answer the question in terms of time on the clock.

Prompt 2: Some patients will give their own blood sugar status. All you can do is repeat the question. The respondent must figure out independently if the data provide the basis for the answer. Remind the respondent to provide a yes/no answer.

Prompt 3: Some respondents will incorrectly give the date for their next appointment. If the respondent does not answer with a date, remind them to provide a date as the answer.

Prompt 4: Remind the respondent to answer the question in terms of time on the clock.

35.4.3 Section C: Reading Comprehension Assessment Instructions

The reading comprehension assessment contains 36 reading comprehension items in two (2) passages. These passages test understanding of health care texts such as preparation for a diagnostic procedure and Medicare Rights and Responsibilities. The respondent is asked to select a correct response from a list of four possible choices and has **7 minutes** to complete the test.

Please make sure that you have a stopwatch and the “Section C Example” prompt card ready before beginning the test.

Read the **bolded** script (in the box on the next page) verbatim to the individual taking the test. The words that are capitalized and not bolded are prompts for you to follow and should not be read out loud. After reading the script, hand the respondent the Reading Comprehension passages to be completed (on the appropriate HLA01 form) and start the timer when they begin the test. After **7 minutes** have elapsed, stop the timer and remove the test materials from the individual.

Reading Comprehension Script

“Do you wear glasses? (IF YES...) Please put them on.

I am going to show you some medical instructions that you might see around a hospital. There are words missing in these instructions, like in this example (HAND PARTICIPANT THE SECTION C EXAMPLE PROMPT CARD).

I want you to fill in the missing words. Just below the blank line, we’ve listed 4 possible words to complete the sentence. Choose the word that makes the most sense. Circle the letter in front of the word you choose.

So, in this example, “Your blood test was blank”, the word “normal” is the only word that can complete the sentence so it makes sense. So, you would circle the letter “a” in front of the word “normal”. Is that clear?

There are four pages, and the page numbers are shown at the bottom of each page. (TURN TO THE FIRST PAGE OF THE TEST AND SHOW THE PAGE NUMBER). Be careful not to skip any.

You will have 7 minutes to do this. Please complete as much as you can in that time.

HAND PARTICIPANT THE FOUR PAGES OF THE TEST ATTACHED TO THE FORM.

START A TIMER WHEN THE PARTICIPANT STARTS THE TEST. STOP THE TEST AT THE END OF 7 MINUTES AND REMOVE TEST MATERIALS FROM THE PARTICIPANT.

Ready? You can start.”

35.5 SCORING OF THE HLA FORM

The HLA form will be scored centrally at the Clinical Coordinating Centers (CCCs). Sites should send completed tests back to the CCCs with their binders. The CCCs should score HLA form using the Health Literacy Coding Sheet (HLC01).

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SECTION 36: STANDARDS OF PROCEDURES AT REPOSITORIES

36.1 OVERVIEW OF REPOSITORIES

There are two repositories which store samples:

- NIDDK has contracted with the Rutgers University Cell & DNA Repository (RUCDR, Genetics Repository) to establish cell lines or to extract PBMC's and DNA from whole blood. Whole blood for cell lines, or for DNA and PBMC extraction, are shipped immediately upon collection to the repository at Rutgers.
- NIDDK has contracted with the Fisher Bioservices to establish a NIDDK biological repository for the long-term storage of blood, urine, hair samples and nail clippings. Samples are processed, frozen or ambient and then shipped via licensed overnight carrier quarterly to the NIDDK Biological Repository.

36.2 COLLECTION AND SUBMISSION OF SAMPLES

At Visit 1b, blood, serum, plasma and urine samples are collected. Whole blood for the DNA Repository, and hair and nail samples for the Biological Repository are also collected at V1b. (Refer to Section 11: Sample Handling and Shipping MOP for more information on how samples are collected, handled and shipped to the repository.)

Each sample is coded with a NIDDK ID number. The **NIDDK-ID#** is unique. The entire NIDDK-ID# consists of the center (i.e., study) ID assigned by the repository (543) followed by the CKiD identification number (KID ID number which consists of the cohort number, site number and subject ID number). For example, if a child at site 68 is assigned the ID number 001 during the first phase of enrollment, the NIDDK-ID# will be: 543-1-68-001

36.2.1 Collection of Whole Blood for the Genetic Repository

- The RUCDR provides preassembled collection kits to the Central Biochemistry Laboratory (CBL). The kits includes:
 - instructions
 - a collection form
 - Vacutainer blood collection tubes with linear bar code labels
 - packaging that meets federal
 - IATA and state regulations
 - a pre-addressed Federal Express airbill directing shipping and billing to the RUCDR.

- After the initial shipment of RUCDR kits, additional kits are provided upon request. Judith Jerry-Fluker requests additional kits for the CBL

Study	Kit Configuration
CKiD	Three pediatric ACD tubes for all age groups Modified Domestic and International kits
*Standard Domestic kits contain: Three 8.5ml ACD tubes #Standard International kits contain: Two sets of three 8.5ml ACD tubes	

- The CBL provides sites with the collection kits. During the appropriate study visit, the site collects samples in the Vacutainer collection tubes pre-labeled with linear bar codes. Sites add NIDDK subject codes to the tubes, being certain not to cover the bar code label.
- At no time should blood collection tubes or data collection sheets include personal identifiers of the subject.

36.2.2 a. Collection of Samples for the Biological Repository

The Fisher Biological Repository provides preassembled collection kits to the CBL. Urine, serum, plasma, hair and nails are shipped to the Fisher Biological Repository. For details on the collection and handling of these samples, refer to Section 11 of the CKiD MOP.

36.3 SHIPMENT OF SAMPLES

36.3.1 Shipment of Samples to RUCDR

- Blood samples are shipped to the RUCDR by Federal Express priority overnight. Shipping is at ambient temperature in the supplied Styrofoam insulated blood mailers approved for blood shipment. Samples should be shipped the day of collection so that samples are received at the RUCDR as soon as possible to ensure that the cells remain viable for transformation.
- Prior notification of incoming samples must be provided to the RUCDR on the day of shipment.
- Prior notification includes the NIDDK# of each sample being shipped and the Federal Express tracking number.
- See Section 11 of MOP for additional information on shipment requirements.

36.3.2 Shipment of Samples to Fisher Biological Repository

- See Section 11 of MOP for specific information on shipment requirements for each type of sample. The following samples are shipped to Fisher:
 - Serum samples are shipped to Fisher
 - Plasma samples are shipped to Fisher
 - Urine samples are shipped to Fisher
 - Hair samples are shipped to Fisher
 - Nail clippings are shipped to Fisher
- Prior notification of incoming samples must be provided to the Fisher on the day of shipment.
- Prior notification includes the NIDDK# of each sample being shipped and the Federal Express tracking number.
- See Section 11 of MOP for additional information on shipment requirements.

36.4 RECEIPT, INSPECTION AND LOGGING OF SAMPLES

36.4.1 Receipt, Inspection, and Logging of Blood Samples at RUCDR

- When packages arrive at the RUCDR, the packages are inspected for correct labeling and packaging integrity.
- A unique in-house Rutgers ID # (RUID #) is assigned as samples are received at the RUCDR (*e.g.* Kxxxxx or DKxxxxxxx). This RUID # for each sample is used to track the sample throughout processing, transformation and DNA extraction.
- Each subject's blood sample is logged into the secure RUCDR LIMS database with all coded identifiers provided by the clinical site, the RUID#, and the volume of blood received. The NIDDK ID# and the RUID# are cross-referenced in the database.
- The Site Coordinators are notified by email on the day samples arrive at the RUCDR. If any problems with the sample(s) are identified, it is reported as well. In each case that a sample is determined to be unacceptable for processing, the Site Coordinators are notified of the reason(s) for not accepting the sample.
- If there are any discrepancies, the Site Coordinator will be notified by email.
- The Alternate ID # is not entered into the clinical or genetic databases. It is used solely by the RUCDR as a secondary ID to help resolve labeling discrepancies that may occur during sample collection and submission.

36.4.2 Receipt, Inspection, and Logging of Blood Samples at Fisher Biological Repository

- When a package arrives at Fisher, the pre-shipping notification is matched to the corresponding package. The tracking number on the notification is compared to the tracking number on the package and the outer container is inspected for damage.
- The shipper is opened. Any documentation retrieved from the shipper is attached to the pre-shipping notification form.
- The inner package is inspected to ensure there is no breakage, leakage, or thawing of samples. A sufficient amount of dry ice should remain.
- Bags or boxes of samples are removed from the shipper and counted. The bags or boxes of specimens are labeled with the study name and date received, and placed into their designated storage location - ambient or frozen (-80°C) as appropriate.
- The pre-notification form/shipping manifest is stamped as received with the study name, initials of the receiving staff, the date received, number of boxes, and freezer/shelf/rack location or other temporary storage location.
- A unique receipt number is created for the shipment prior to entering the samples into the database.
- The specimens received are verified against the samples listed on the shipment form (Form ST03a). The sample ID, draw/collection date, visit, and sample type on the specimen labels are verified against the information on the shipment form.
- Samples are entered into the database and placed in their permanent storage location - frozen aliquots in the designated -80C freezer and hair and nail clippings in the ambient storage cabinet.

36.5 PROCESSING OF BLOOD SAMPLES AT RUCDR

36.5.1 Establishment of EBV Transformed Lymphocyte Cell Lines (LCLs)

36.5.1.1 Culture Initiation and Cell Line Establishment:

- The whole blood is centrifuged in the Vacutainer tubes; the buffy coat (WBC layer) is removed and resuspended in RPMI-1640 (Corning or Sigma) containing PS and L-glutamine (GIBCO BRL, Life Technologies).
- If the blood is hemolyzed, no attempt at transformation is made, and the submission site is notified that a redraw is requested. Blood will instead be submitted for whole blood DNA extraction directly (*see Section 36.5.4.2 Automated DNA Extraction from Whole Blood*).
- The lymphocytes from this mixture are then separated by centrifugation on a gradient of Nycoprep (Axis-Shield PoC AS, Oslo, Norway) for 30 minutes.
- The lymphocyte layer at the Nycoprep/RPMI-1640 interface is removed and washed twice with RPMI-1640 containing PS and L-glutamine.
- The EBV stock is prepared on-site by sterile filtration of medium obtained from B95-8 marmoset cell cultures (Source; ATCC).
- After the final wash the lymphocytes are resuspended in cell culture “transformation medium”. The “transformation medium” is composed of RPMI-1640, fetal bovine serum (FBS), PS; phytohemagglutinin (PHA), and Epstein-Barr virus (EBV) supernatant. This transformation medium is then transferred to a flask containing a feeder layer of adherent CCL-171 cells.
- One culture is set up for each blood sample.
- The cultures are placed in a HEPA-filtered, humidified incubator at 37°C with 5% CO₂.
- Cultures are incubated for five to seven days before being split into two duplicate cultures with RPMI-1640 medium supplemented with FBS, PS, and L-glutamine (without feeder cells). At this point the duplicate sets of cultures are placed in separate incubators, are maintained by independent technicians, and supplemented with media from separate sources.
- Cultures are checked twice weekly thereafter and supplemented with fresh culture medium as needed.
- Approximately four to six weeks after initiation the cultures begin to demonstrate high density actively growing cell aggregates.
- The cultures are then used to establish expansion cultures for cryopreservation and DNA extraction.
- Cultures with high density healthy cell aggregates are used to inoculate a T-75 flask containing RPMI-1640, bovine calf serum (BCS) (without antibiotics). This final cell culture expansion prior to cryopreservation is in the absence of antibiotics so that any adventitious agents can be detected if present.
- These cultures are incubated for approximately one to two weeks to grow a sufficient number of viable cells for cryopreservation.
- Two separate T-75s for each cell line will be cryopreserved as two independent freezes. The supervisory staff routinely screens all cultures under an inverted phase contrast microscope for the presence of bacterial contamination prior to cryopreservation.

36.5.1.2 Culture Expansion for DNA Extraction:

- During the final culture expansion phase (see above), the cell suspension is used to inoculate a T-175 culture flask in RPMI 1640 supplemented with BCS, PS and L-glutamine. Further expansion utilizes RPMI-1640 supplemented with FBS and L-glutamine.
- The T-175 cultures are incubated for one to one and a half weeks to grow $\geq 1.5 \times 10^8$ cells.
- Each culture is then collected into a single pre-labeled barcoded 50 ml centrifuge tube.
- The cell suspension is then routed to the DNA lab for DNA extraction (*see Section 36.5.4.1 Automated DNA Extraction from LCL Cell Pellet*).

36.5.1.3 Cryopreservation of EBV Transformed LCLs:

- When the cells are ready for cryopreservation, they are transferred to sterile pre-labeled barcoded 50 ml tubes, centrifuged and resuspended in cryopreservation medium.
- One ml of cell suspension containing approximately $5-10 \times 10^6$ cells/ml is dispensed into each prelabeled glass ampule.
- Each ampule has a 2D barcode printed on its bottom surface during manufacture (as a secondary identifier in case of label detachment or illegibility) and all ampules for a particular cell line will be barcode labeled as the cell lines are being processed for freezing.
- The ampules are then flame-sealed with an acetylene gas burner using a motor driven custom-fabricated automated glass ampule sealer.
- The ampules are placed in the chamber of a Planer Kryo 10/16 or Thermo Forma Cryomed controlled rate freezer, equilibrated to 0°C and frozen slowly at -1.0°C per minute down to -30°C . After equilibrating at -30° for 15 minutes, the temperature is dropped to -100°C at -7.0°C per minute.
- After the ampules have equilibrated at -100°C , they are transferred to the liquid nitrogen storage freezers.
- At the time the ampules are being frozen, the freezing location data, which includes cell line identifiers and location, are assigned in the RUCDR LIMS database.
- Nine ampules are cryopreserved for each cell line (two independent freezes). Three ampules from each cryopreservation are stored in two separate main liquid nitrogen freezers and one ampule from each independent freeze is stored in liquid nitrogen at a secondary (back-up) location on-site. The additional ampule are shipped to the Biosample Repository (Fisher) as a redundant back up facility.
- Shipping of frozen LCLs to Fisher take place periodically, depending on the number of samples.
- One ampule from each cell line is thawed and returned to culture for viability testing within two weeks of cryopreservation.

36.5.2 Untransformed Lymphocyte Cryopreservation

- Additional Vacutainer blood tube(s) from each sample other than those used to make LCLs or for DNA extraction will be processed to make cryopreserved untransformed lymphocytes.
- The cryopreserved cells are used for a second attempt in the event of failure of the initial transformation culture. (*See Section 36.5.1.1 Culture Initiation and Cell Line Establishment starting at 4th bulleted statement*).
- As samples are logged in by the data management staff each set of tubes are placed in a test tube rack at the login station.
- A lab technician verifies all identification material on each tube against the prior notification form and the sign-in log.
- The technician ensures that the barcode label on each tube matches the RUID# assigned to that NIDDK ID#.
- Once review is complete, the samples are taken into the cell culture processing labs along with the pre-printed barcodes for each sample.
- The whole blood is centrifuged in the Vacutainer tubes; the buffy coat (WBC layer) is removed and resuspended in RPMI-1640 (Corning or Sigma) containing Penicillin/Streptomycin solution (PS) and additional L-glutamine (Gibco, Life Technologies).
- The lymphocytes from this mixture are then separated by centrifugation on a gradient of Nycoprep (Axis-Shield PoC AS, Oslo, Norway) for 30 min.
- The lymphocyte layer at the Nycoprep/RPMI-1640 interface is removed and washed twice with RPMI-1640 containing PS and L-glutamine.
- The isolated, washed lymphocytes are resuspended in cryopreserving medium, cryopreserved, and stored in liquid nitrogen.

36.5.3 Freezing of Additional Ampules for Depleted Stocks

- A minimum of five FVC ampules for each cell line are maintained in main storage at any one time.
- At least two ampules are stored in a backup location(s).
- In the event ampules are removed for regrowth and/or distribution and the inventory drops to five ampules, a culture are initiated for preparation of additional ampules.
- Procedures for initiating a culture and subsequent replacement cryopreservation are as described above.

36.5.4 Genomic DNA Extraction

36.5.4.1 Automated DNA Extraction from LCL Cell Pellet

- The Qiagen Autopure LS protocol for LCL cell pellet DNA extraction is used to extract DNA. This instrumentation utilizes Puregene salting out chemistry to enable automated purification of DNA from large volume samples.
- The DNA yield from transformed cell line pellets is approximately 1,500 to 2,000 µg per 2×10^8 cultured cells, and the A_{260}/A_{280} ratio is in the range 1.9 to 2.0 O.D.
- DNA is aliquoted into four 2D bar code tubes, and frozen @ -80°C until requested; data is stored in the RUCDR LIMS database.
- DNA extracted from LCL cell pellets can be made available within two to three weeks from the time of receipt.

36.5.4.2 Automated DNA Extraction from Whole Blood

- Following the sample receipt process, any compromised blood tubes (*e.g.*, hemolyzed samples) are centrifuged at 3000 rpm for 10 minutes and plasma is removed.
- All DNA extractions from whole blood are performed on Hamilton Chemagic Star instruments using a magnetic bead-based chemistry, which offers a scalable combination of kits and protocols to effect rapid (2.5-4 hours), automated extraction of DNA from whole blood.
- The extracted DNA is stored in one 2D bar-coded tube and frozen at -80°C until requested; data is stored in the RUCDR LIMS database.
- The DNA yield from whole blood is dependent on the volume of the initial blood sample and the number of white blood cells present in the sample (approximately 25-30 µg per ml of whole blood from a participant in good health).
- DNA extracted directly from whole blood can be made available within two to three weeks from the time of receipt.

36.6 PROCESSING OF SAMPLES AT FISHER BIOLOGICAL REPOSITORY

- Fisher Management receives the sample list and details for aliquoting of frozen blood and urine samples from the Data Management Repository (DMR).
- The samples to be aliquoted are retrieved using the pull/sample list.
- A second person scan checks and/or performs a manual 100% sample check to confirm the correct samples have been pulled. If there is a discrepancy, the DMR or the Study Coordinator is notified.
- Parent tubes are stored in a temporary freezer location until they are ready to be aliquoted.
- Labels are created for child cryovials and applied to cryovials prior to aliquoting specimens.
- The biological safety cabinet is disinfected.
- The required volume of each specimen is aseptically transferred into the pre-labeled cryovial.
- When aliquoting is complete, all cryovials are verified that they are securely closed and removed from the process area.
- Child vials are entered into the inventory management database and placed into their permanent storage locations.
- A data file with the information for the child vials is created and uploaded to the database (sample ID, collection date, visit, sample type, size, thaw count, aliquot date, and parent ID).
- If the parent tubes are totally empty, they are discarded and shipped from the database. If parent tubes have remaining samples in them, they are placed into a permanent location and their freezer location, size and thaw count are updated in the database.

36.7 RUCDR QUALITY CONTROL

36.7.1 DNA Processing

DNA sample identity and integrity are assured by:

- Logging in of individual samples upon receipt and contemporaneous establishment of computer records.
- Barcode labeling of Vacutainer blood collection tubes, and labeling of all tubes used during sample processing.
- Checking the identification material on each tube before processing.
- Application of rigorous analytical procedures to check DNA integrity, quantity, and quality. All data is maintained within the RUCDR LIMS database.
 - Trinean DropSense96, used to generate spectroscopic data in order to calculate DNA concentration and A_{260}/A_{280} ratios.
 - VolumeCheck instruments are used to measure solution volumes using a non-contact ultrasonic technology.
- Careful attention to detail during the entire extraction process.
- Handling only one DNA/Plasma sample at a time in a laminar flow hood.
- Error checking functions built into the database tracking system.

36.7.2 Verification of Pedigree Relationships

- Archival blood samples are routinely stored with a DNA preservation reagent indefinitely.
- Identity testing is done using DNA comparisons using a proprietary RUID™ panel containing 96-SNPs developed by RUCDR.
- A request that blood be redrawn will be sent whenever there is any unresolved question as to the identity of a sample.

36.7.3 Quality Assurance

As a part of this program, a log is kept on a monthly basis of the following parameters:

- Samples from which insufficient DNA was obtained.
- DNA samples showing unacceptable A_{260}/A_{280} absorbance readings.
- Technical or clerical errors.
- Whenever a QC problem is identified, immediate corrective action is taken by the supervisor of the DNA laboratory in consultation with the Chief Operating Officer of the RUCDR.
- A record is also kept of samples showing unusual genotype or inheritance patterns, and every effort is made to resolve these patterns.

36.8 FISHER BIOLOGICAL QUALITY CONTROL

- QC staff creates a weekly inventory report for the CKiD Study for any samples entered during the previous week.
- QC staff compares the information (sample ID, collection date, visit, sample type) on the shipping form against all data entered into the inventory database (sample ID, collection date, visit, sample type) using the weekly inventory report.
- QC staff verifies that the samples are stored in the correct designated storage area.
- QC staff notes any discrepancies on the report and notifies Fisher Management.
- If there is discrepancy, Fisher Management notifies the site and DCC by e-mail to resolve the discrepancy.
- When the answer is received, proper corrections are performed.

36.9 SHIPMENT/RECEIPT REQUIREMENTS AND SCHEDULES OF DNA SAMPLES FOR ANCILLARY STUDIES

36.9.1 Shipment of DNA Samples

- Approved requests for DNA samples are shipped within two weeks (four weeks for requests exceeding 100 samples, possibly longer for special requests; *e.g.* specific sample order, special plates, *etc.*).
- The RUCDR utilize an NIDDK-approved Material Transfer Agreement for the distribution of all biomaterials.
- The applicable data files for cross-referencing the original sample ID# with the RUID# are sent electronically in an Excel file.
- DNA samples can be shipped on dry ice or at ambient temperature as per requesting investigators' recommendation.

36.9.2 Distribution of Cryopreserved Transformed Cell Lines

As of 2015, no live LCLs have been shipped to any investigators; however, investigators can request them. In the event that live LCLs are requested, the process to ship the samples is as follows:

- Transformed LCL's can be shipped live (in culture) at ambient temperature, frozen on dry ice, or frozen in a dry LN₂ shipper to the requesting investigator depending on a number of factors (*i.e.* facilities at requesting investigators lab, the number of LCLs requested, the distance and transit time of shipping, *etc.*).
- An ampule for each sample requested is removed from one of the main storage tanks and the date of removal recorded in the RUCDR LIMS database.
- Live cultures will be distributed to investigators having the expertise to manipulate and maintain the LCLs in culture.
- Frozen LCLs will be shipped to requesting investigators that have liquid nitrogen storage vessels available for storage of the frozen LCLs.

- Live cell cultures for distribution may be initiated from cryopreserved LCLs after an approved (*i.e.* approved by the NIDDK PO) request list is received by the RUCDR NIDDK Communications Coordinator.
- If the granting or contracting agency has not waived the fee for the cell line (or DNA), an invoice will be sent to the requesting investigator. The request will not be processed until payment is received unless otherwise approved by the NIDDK PO.

36.9.3 Shipping and Receipt of Frozen EBV-Transformed Lymphocyte Cell Lines (LCLs)

- Frozen LCLs sent to and distributed from the RUCDR may be shipped in a MVE LN₂ vapor cryo-shipper provided by the RUCDR (IATA/DOT/UN/FAA approved).
- The shipping system has a high impact resistant outer shell, dry vapor shipper and stainless steel inner sample core.
- All domestic shipments will utilize FedEx as the shipping agent.
- The shipper has a built in computer monitoring system that records the internal temperature of the dewar throughout the shipping process.
- The capacity of the dewar is 400 ampules or vials contained in four cryoboxes of 100 vial capacity.
- All shipping instructions, packaging instructions, absorbent pads and a return FedEx shipping label will be supplied by the RUCDR to the NIDDK approved investigator.
- Ampules containing frozen LCLs will be shipped within two weeks of request.
- For incoming shipments to the RUCDR, the investigator will supply a hard copy of the sample inventory with the shipment and email an Excel spreadsheet containing the inventory to the RUCDR upon shipment.
- LCLs will be shipped to the RUCDR by Federal Express priority overnight.
- Prior notification of incoming samples should be provided to the RUCDR on the day of shipment by email.
- Prior notification will include the NIDDK# of each sample being shipped and the Federal Express tracking number.

36.9.4 Quality Assurance Program

- As part of our Quality program, a log is kept of the following parameters:
- Blood samples arriving late or in poor condition.
- Unsuccessful transformations.
- Cell line contamination.
- Technical or clerical errors.
- Turnaround time for distributions of live cultures.

36.10 SHIPMENT OF BIOLOGICAL SAMPLES FOR ANCILLARY STUDIES

36.10.1 Shipment of Urine, Serum, Plasma, Hair and Nail Samples

1. The NIDDK BioSample Repository receives an email notification from the NIDDK Data Repository when a client request for specimens has been approved and is ready for processing.
2. Repository management logs into the NIDDK website, downloads the request list and retrieves all necessary documentation provided.
3. A repository manager checks if the shipment requires any aliquoting. If the request requires aliquoting, the manager obtains the aliquoting information from the NIDDK Data Repository or DCC (for example, size of the child vials, or # of vials that needs to be created from the parent vial).
4. The repository manager generates a pull list for the specimen request and assigns the pull list to a repository technician.
5. The pulling technician verifies information on the vial labels against information on the pull list to confirm the correct specimens are pulled, and informs the manager of any issues noted. The manager corrects any discrepancies.
6. A second staff member performs a 100% barcode scan check of the vials pulled against the pull list. If no barcode is present, a 100% manual check is performed of all vial label information compared to the pull list. Staff returns the pull list to the manager and informs the manager of any issues noted. The manager corrects any discrepancies.
7. If the shipment requires aliquoting, the NIDDK Repository follows the procedures noted in section 36.6. After aliquoting is completed, a final scan check is performed and the requested vials are placed into a temporary storage location until the shipment date.
8. A manager sends the final packing list to the NIDDK Data Repository for a QC check. If the file is correct, the manager confirms the shipment address and shipment date with the requestor.
9. All frozen plasma, serum and urine specimens are shipped on dry ice; hair and nail samples are shipped in ambient shippers. Specimens are shipped via FedEx Priority Overnight, FedEx International Priority, or World Courier.
10. Domestic shipments are only shipped Monday through Wednesday. International shipments are shipped Monday or Tuesday.
11. The manager sends an email to the requestor with an electronic copy of the shipping log and a tracking # for the shipment on the day of shipment.
12. The manager updates the repository inventory database to note that the specimens were shipped and are no longer available.
13. The manager uploads the final packing list to the NIDDK website and provides the final shipping address to the NIDDK Data Repository.
14. The manager confirms the shipment was received by the requestor.

36.11 TIME PERIODS FOR COMPLETION OF SERVICES

36.11.1 Time Periods for Completion of Services by RUCDR

The time schedules for completion of following services are based on the budgeted number of samples, but should not change with increased numbers of samples. These schedules present the time frame within which the indicated services will be completed for at least 90% of samples. In many cases, the time required will be less than indicated.

a. LCL Transformation and Cryopreservation from Whole Blood

- From the time of receipt of whole blood, approximately two and one half to three months are required for the majority of samples to be transformed, cryopreserved, and viability tested.
- Approximately 96% of successful LCL transformations are cryopreserved within 90 days of receipt of blood.
- If successful cultures are not obtained from a sample within four months it will be noted as a failure and appropriate notifications made.

b. DNA Extraction

- LCLs must undergo transformation and cell expansion prior to DNA extraction.
- DNA from transformed LCL cell pellets will be extracted on most LCLs (>95%) within three months of initiation of cultures.
- DNA extracted directly from whole blood, if performed, is completed within 24 hours of sample receipt.
- DNA samples can be made available for distribution within two to three weeks of the extraction date.

36.11.2 Time Periods for Completion of Services by Fisher Biological Repository

For pull requests, the repository timelines are as follows:

1-100 vials-1 business day
101-500 vials 4 business days
501-1000 vials 8 business days
1001-5,000 vials 37 business days

For aliquoting requests with up to 10 child vials per parent tube:

1-100 vials – up to 5 business days
101-500 vials - up to 20 business days
501-1000 vials - up to 40 business days

These timelines assume all pre-payments are made, all approvals are received, and all discrepancies are resolved. If the requested vials require a manual/visual check of information on the parent tubes against the request list, then the timelines may double. Timelines may also vary depending on the number of requests in progress.

36.12 REMOVAL OF SAMPLE BIOMATERIALS

- The study site will receive the request from the participant that the sample is to be withdrawn from the study.
- The site will forward this removal request to the CCC, who notifies the DCC and the DCC subsequently notifies the Repository.
- When the Repository receives a request to discard specimens, Repository Management sends a confirmation email to the DCC and the NIDDK Project Officer to obtain approval to destroy the specimen.
- Once all the appropriate approvals are obtained, the following occurs:
- At the NIDDK Repository:
 - A pull list is created from the inventory database.
 - A technician pulls the specimen(s) to be discarded.
 - A second person verifies the approvals and verifies the correct specimen(s) were pulled for destruction. The ID on the specimen label is compared to the ID on the original request for destruction.
 - Either the puller or checker places the specimen(s) to be discarded into an appropriate biohazardous waste container.
 - All related documentation (including the request and approvals) are attached to the pull list and filed.
 - If an inventory record of the specimen(s) exists, the database is updated to note that the sample(s) were discarded and are no longer available.
 - An email is sent to the study DCC to notify them that their requested specimen(s) were discarded.
- At the DNA Repository:
 - The NIDDK PO notifies the RUCDR in writing, and all biomaterials are destroyed by off-site incineration following the sample elimination SOP.
 - All associated electronic files will be deleted from the database and all paperwork will be destroyed.

CHRONIC KIDNEY DISEASE IN CHILDREN COHORT STUDY

SECTION 37: ACCELEROMETRY

37.1 ACCELEROMETRY

This section describes the procedures to collect physical activity data using an ActiGraph accelerometer. The purpose of using an accelerometer is to be able to assess physical activity in the participant's regular environment. The ActiGraph will be used to measure physical activity for 8 days starting at V1b and at CKiD study visits every year thereafter. Children who are five (5) years old or older are recommended for the Actigraph study.

Materials and forms needed:

1. ActiGraph (an accelerometer, see picture below)
2. Computer or laptop
3. Padded return envelope
4. ActiGraph Diary
5. Return Instructions
6. Accelerometry Form (Form 20)



For additional information about the ActiGraph device, see Section 37 – Appendices A (ActiGraph GT9X Declaration of Conformity) and B (ActiGraph GT9X Quick Start 2014 Guide).

37.2 REQUESTING AN ACTIGRAPH

ActiGraph devices will be provided by the Data Coordinating Center (KIDMAC). In order to obtain an ActiGraph, the study coordinator must complete the “ActiGraph Request” form via the Coordinator’s Corner of the CKiD Website (see 37.2.1 for details). The study coordinator will explain the purpose of the device, perform device placement, and ensure device is returned from the participant. Upon receiving the ActiGraph back from the participant, the study coordinator should return the device to KIDMAC for download and analysis. The site should follow up with the participant to ensure the monitor is returned promptly.

37.2.1 Steps to Submit ActiGraph Request

1. Go to Coordinator’s Corner on the CKiD website <https://statepi.jhsph.edu/ckid/admin/coordinator.html> and click on the ActiGraph Request link. For your site’s username and password, contact Judith Jerry-Fluker at jjerry@jhu.edu. The form must be completed and submitted at least 5 business days prior to the study visit date to allow sufficient time for the monitor to be shipped out and received at your site.
2. Fill out the following fields on the ActiGraph Request form:
 - Requester’s Email Address
 - Site #
 - Site Name
 - Scheduled Visit Date
 - CKiD ID#
 - Visit
 - Current age
 - Participant Information:
 - i. Rate how likely the family would be to comply with the study protocol (i.e., wear the device consistently and return the device within designated time)
 - Site Contact Information:
 - i. Name of person to contact if there are any questions
 - ii. Address, room # (if applicable), city, state, and zip code of location that the device should be shipped to
 - iii. Phone number of contact person
 - iv. Comments, if applicable
3. Click on the submit button and KIDMAC will receive an email containing your request.
4. KIDMAC will send an email verifying that the request has been received (and may request more information if necessary) and a device will be reserved for the participant’s visit.
5. Your device will be sent via FedEx to you using business 3 day delivery in most cases. In rare cases, if the device is needed urgently, it can be overnighted but this is expensive and consumes the study budget. Therefore, sites are encouraged to request the device in advance such that the device can be shipped using business 3 day delivery. The shipment will contain the following:
 - ActiGraph device
 - ActiGraph Diary (see Section 37.6)
 - Return Instructions (see Section 37.7.2 for Site and Participant Shipping instruction sheets)
 - Padded return envelope for participant to use to return device
 - NOTE: The CCCs will include the Accelerometry Form (Form 20) with the other study forms
 - NOTE: *Charging dock may be included only in rare circumstances.*

6. KIDMAC will contact you if any information is missing or if the physical activity monitoring was unsuccessful and should be attempted again.

37.3 ACTIGRAPH INITIALIZATION PROCEDURE *(Performed by KIDMAC ONLY)*

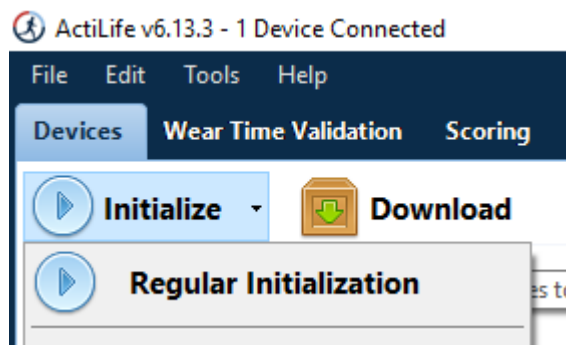
Prior to shipping the ActiGraph to the site, KIDMAC will initialize the device. Initializing the ActiGraph is a critical part of the accelerometry data collection. The ActiGraph must be initialized prior to placing on the participant's wrist. Unique initialization is performed for each participant for the date of the scheduled visit. **In the event that the visit is rescheduled or the device is not used, KIDMAC should be notified and the device must be returned to KIDMAC immediately.** It cannot be used for another participant or kept for a future visit.

KIDMAC will use the following guidelines to complete the initialization procedure.

1. Plug the charging station (dock) into the PC using the USB cable which will be used to both charge and initialize the device. Place the ActiGraph firmly into the charging station.
2. Make sure the computer is on to allow for charging.
3. Record the ActiGraph serial number (the number under the bar scan) in the tracking database.

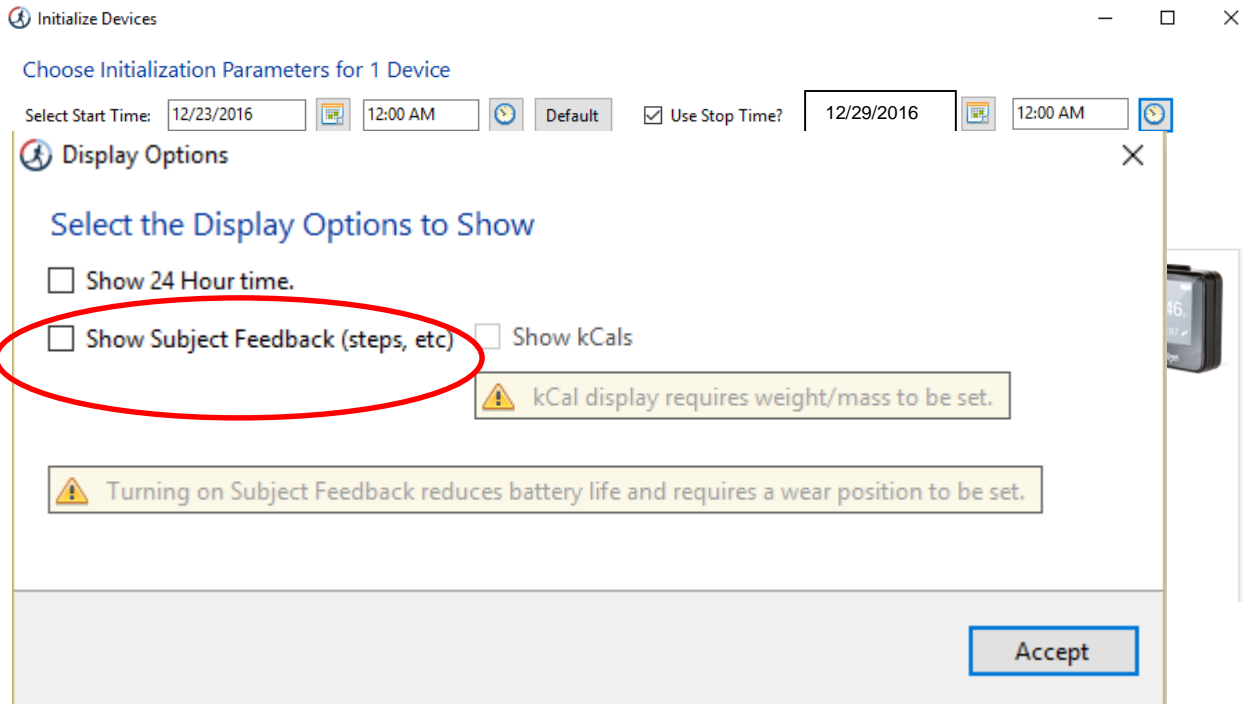


4. Open the ActiLife software and click the “Devices” tab.
5. Click “Initialize”.
6. Click “Regular Initialization”.



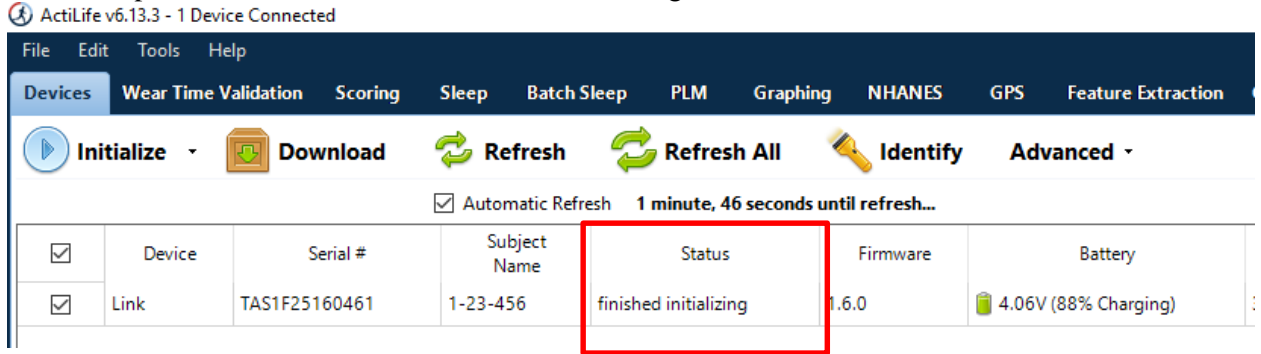
On the “Initialize Devices” pop up menu:

- Select the **desired start time**. If you want to have exactly 7 days of data (for easier data processing) set the start time to be midnight after the CKiD visit is scheduled (12:00 am the next day)
- Check “Use stop time”. Select stop time to be at **11:59pm 7 days** from the start time.
- Set sample rate to be 80 Hz
- Check “Show Display”
- Click “Options”



- Click “Accept” *Note:* If “Show Subject Feedback (steps, etc.)” box is checked, then it should be unchecked prior to clicking “Accept”.

8. When complete, the status will read “Finished initializing”.



9. Once the device has finished initializing, remove the device from the charging station. Place the device in a wrist strap.

37.4 PRIOR TO PLACING THE ACTIGRAPH ON THE PARTICIPANT

37.4.1 On the day before the visit:

1. The CKiD coordinator should compare the monitor # on the device to the monitor # recorded on the Accelerometry Form (Form 20) and the ActiGraph diary. The monitor # is the last 4 digits of the ActiGraph’s serial number, which is located under the bar scan.

For example, the monitor # for the device below is **0017**.



2. Check the battery life. KIDMAC will charge the device prior to shipping but some battery life may be lost in transit. If necessary, a charging dock will be provided so the device may be charged on site. Battery life can be checked on the top right corner of the watch face. The picture below shows an acceptable battery life for study use.



The ActiGraph should be fully or close to fully charged prior to placing it on the participant. In rare cases, KIDMAC may provide a charging dock in the rare event that the site receives the monitor several days prior to the study visit. If a site receives a charging dock, use the charging dock and ActiGraph USB cable sent by KIDMAC. It is very important to use the ActiGraph USB cable. **Failure to do so could lead to device failure and possibly fire.** Picture below shows device being charged in charging dock.



37.5 PLACING THE ACTIGRAPH ON THE PARTICIPANT

37.5.1 On the day of the visit:

1. Check the battery life.
2. Complete Accelerometry Form (see Appendix Section 37 A “Accelerometry Form”)
3. Prior to placing the device, sites should ensure that the following eligibility criteria are met:
 - The participant has the ability to walk unassisted (i.e. without crutches, cane, leg braces, wheelchair)
 - The participant has at least one hand without visible limitations (i.e., wearing cast/bandage, missing digits, paralysis)
4. Ask the participant to remove hand and wrist jewelry.
5. **Preferably at the beginning of the visit**, introduce the ActiGraph to the participant. Below is a suggested script for introducing the device to the participant.

The investigators would like to see how physical activity is related to kidney disease. To collect information about how much you move during your regular day, we would like you to wear a special watch called an ActiGraph accelerometer as much as possible during the next 8 days. This watch will tell you the time, but it will not show you how active you are.

37.5.2 Instructions for Participant

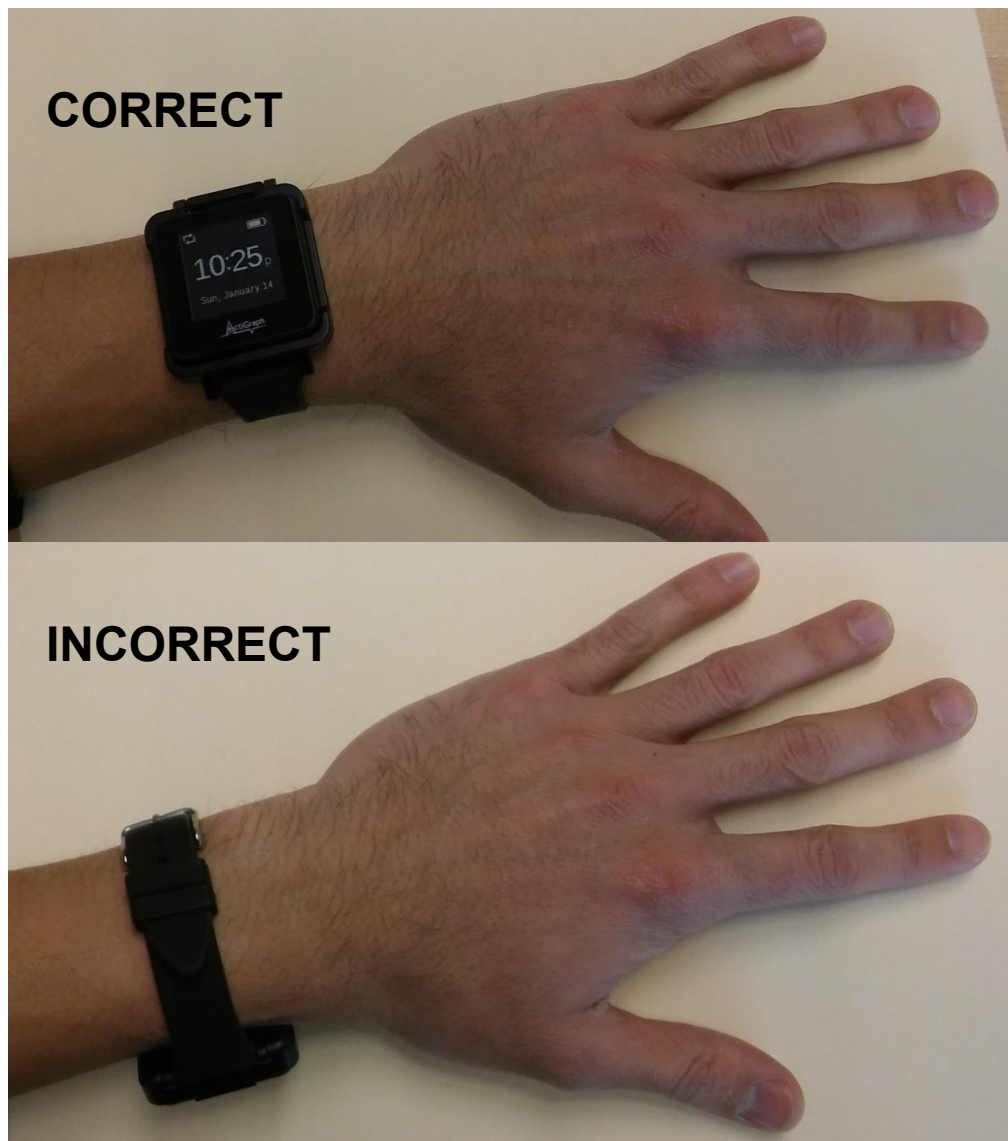
Review the ActiGraph diary (see Section 37.6 for example of diary) with the participant and answer any questions they may have. Stress that the device is to be worn for 24 hours per day for the next 8 days and to minimize the time it is off the wrist as much as possible. As indicated above, note that participants must record the date and time that they remove the device on the ActiGraph diary and include the diary when they return the device. Give participant the diary and participant return instructions (if applicable). Below is a suggested script for explaining the ActiGraph diary to the participant.

*As I said, please wear this watch as much as possible during the next 8 days. Also, you should take it off if you plan to swim or are instructed to remove it for sports activities, but please put it back on immediately after (showering and short baths are okay with the device on). If you take it off, please write down when you take off the watch and when you put it back on. **IT IS VERY IMPORTANT TO WEAR THE WATCH AS MUCH AS POSSIBLE DURING THE NEXT 8 DAYS** so we may get an accurate picture of how you move on a regular day and how that is related to health. It is also important that you wear it while you are asleep so we get an idea of your sleep pattern and how it is related to health. We will be using these devices for other participants in the study so please take care of it. Every time you take it off is also an opportunity for it to be lost, so please do not take it off unless absolutely necessary.*

On the removal date listed in the ActiGraph diary, place the watch and ActiGraph diary in the padded envelope. You should either bring it back to me or use FedEx to return it.

37.5.3 Placing the Strap on the Wrist

- Place the wrist strap containing the ActiGraph on the participant's **NON-DOMINANT** wrist. **It is preferable that the ActiGraph is worn on the NON-DOMINANT wrist**; however, if the participant prefers, it can be worn on the dominant wrist. Regardless of which wrist the device is worn, it is imperative that the site documents on the Accelerometry form (F20) which wrist the device is placed.
- Preferably, device placement should occur in the early part of the visit to identify any issues the participant may have with wearing it.
- The device should face upward and should not be rotated down so that it is facing the palm.




37.6 ACTIGRAPH DIARY AND ACTIGRAPH LETTER

37.6.1 ActiGraph Diary

KIDMAC will fill in the Study ID, CKiD visit and monitor # as well as the date of removal (Item #3 of the diary, i.e. the time when the device may be removed and returned). When the device is finished collecting data, the watch face will switch from the time to a STOP hand: This will let the participant know that it is time to return the device.



Please review the diary with the participant and ask if they have any questions.




Actigraph Diary


Study ID #	_ _ - _ _ - _ _
CKiD VISIT #:	_ _ - _ _
MONITOR #:	_ _ - _ _

Thank you for agreeing to wear the Actigraph physical activity monitoring device. During the visit, your CKiD study coordinator will place the Actigraph on your non-dominant wrist to make sure it fits comfortably with no problems. After the visit, if you have questions or concerns about the device please contact your clinical site coordinator.

Please follow the instructions:

- Please wear the Actigraph device (as shown in photo) at all times for the next eight (8) days (**see date listed in step #3**).
If you plan to swim, you should remove the device during that time. Immediately after you finish swimming, put it back on. (Showering and short baths are ok). 
- If you must temporarily remove it for any reason (including swimming, sports activity etc.), please complete the table below. An example is provided.
 - Write the date and time the device was removed from your wrist.
 - Write the date and time when the device was put back on your wrist.

Date	Time Removed	Time Replaced	Reason for removal
M M / D D / Y Y	AM / PM	AM / PM	(e.g. Swimming lesson)
M M / D D / Y Y	AM / PM	AM / PM	
M M / D D / Y Y	AM / PM	AM / PM	
M M / D D / Y Y	AM / PM	AM / PM	
M M / D D / Y Y	AM / PM	AM / PM	
M M / D D / Y Y	AM / PM	AM / PM	

- On the last day, when the device face has a STOP hand on it, you should take off the device and put it back in the package you received from your clinical site. You should wear the device until:
Date and time: |_|_| / |_|_| / |_|_|_|_| (remove device when you wake up) 
- Please note the exact day and time you removed the device:
Date and time: |_|_| / |_|_| / |_|_|_|_| : |_|_| AM/PM
- To return the device, follow the shipping instructions.

37.6.2 ActiGraph Letter

During the academic school-year, participants who are attending school will be asked to wear the ActiGraph device to school. Study Coordinators should provide the family with a letter for the participant to take to school. Below is an example of the family ActiGraph letter that will be included with each monitor shipped. Write in the date, participant's date of birth and participant's name. This letter can be sent by email if requested.



Date:

RE: ActiGraph Physical Activity Device

DOB: _____

To Whom It May Concern:

_____ is currently wearing an ActiGraph Physical Activity device. The device is worn on the wrist and should be worn at all times. She/he may participate in her/his usual activities (including gym class or sports practice) while wearing the device.

Please feel free to contact us if you have any questions about this matter.

Sincerely yours,

Division of Pediatric Nephrology

37.7 ACCELEROMETRY FORM (F20)

Participants or their parents should complete the F20 form with the coordinator. Please ask them to bring their calendar of upcoming activities to the visit, as this will make filling out this form easier.

ACCLEROMETRY (F20)				
+ A9. b. Please specify why the Actigraph device was not given to the participant (Circle "yes" to all that apply):				
		Yes	No	
1.	Participant/Family refused.....	1	2	
2.	Scheduling difficulties.....	1	2	
3.	Site decision (participant not good candidate).....	1	2	
4.	Other.....	1	2	→ (END FORM)
i. Specify:				

The following procedure should be followed if the participant is to wear the ActiGraph:

1. Provide the participant with instructions (refer to MOP Section 37)
2. Ask participant to remove hand and wrist jewelry, and demonstrate how to place the device

SECTION B: HANDEDNESS

B1.	Are you right-handed, left-handed, or do you use both hands equally?	
	Right-handed.....	1
	Left-handed.....	2
	Use both hands equally.....	3
	Too young to determine.....	4
	Don't Know.....	-8
B2.	We prefer you wear the watch on your other hand (i.e., non-dominant hand), but you may wear it on whichever hand you choose as long as you don't switch hands. On which hand do you prefer to wear the watch?	
	Left.....	1
	Right.....	2

SECTION C: ACTIVITY

C1.	Do you have school or work in the coming week?	
	Yes.....	1
	No.....	2 (Skip to C4)
C2.	Please specify which days you will be attending school or work (please select all that apply):	
a.	Monday.....	1
b.	Tuesday.....	2
c.	Wednesday.....	3
d.	Thursday.....	4
e.	Friday.....	5
C3a.	When does your typical school or work day begin? The school or work day would begin when you leave your house.	
	_____ : _____ 1 = AM 2 = PM	
C3b.	When does your typical school or work day end? The school or work day ends at the time when you return home.	
	_____ : _____ 1 = AM 2 = PM	
C4.	Do you participate in structured activities outside of school or work?	
	Yes.....	1
	No.....	2 → (END FORM)

For questions C3a and C3b, if school or work days begin and end on different days, please use the average for the week. For example, if a participant returns straight home from school for three days at 3pm, but goes to after-school care for two days and returns home at 5pm, please indicate 4pm as the typical school end time.

The sample calendar at the end to track sedentary to highly active activities should be reviewed prior to filling out C5. The coordinator should note that the participant or families do not have to disclose what the activity is, but rather how much the participant will be moving during that time. Please use only whole numbers to describe the activity (1 or 2 should be selected, not 1.5).

C5. Please specify when structured activities occur outside of the school or work day in the upcoming week and how physically active you would rate each activity (please draw boxes for when each activity occurs and write in the level of activity). Examples of activities include sports, dance, community programs, church, work (if a student), or other after school programs. See example schedule on last page.

Activity Codes:

1= Sedentary (e.g., sitting/reading)	3 = Moderately active (e.g. lots of walking)
2 = Minimally active (e.g. some walking)	4 = Highly active (e.g., sweating, heavy breathing)

Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
6:00 AM							
6:30							
7:00							
7:30							
8:00 AM							
8:30							
9:00							
9:30							
10:00							
10:30							
11:00							
11:30							
12:00 PM							
12:30							
1:00 PM							
1:30							
2:00							
2:30							
3:00							
3:30							
4:00							
4:30							
5:00 PM							
5:30							
6:00							
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8:00							
8:30							
9:00							
9:30							
10:00							
10:30							
11:00 PM							
11:30							

Sample calendar

Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
6:00 AM							
6:30							
7:00							
7:30							
8:00 AM							
8:30							
9:00							
9:30							
10:00							
10:30							
11:00							
11:30							
12:00 PM							
12:30							
1:00 PM							
1:30							
2:00							
2:30							
3:00							
3:30							
4:00							
4:30							
5:00 PM							
5:30							
6:00							
6:30							
7:00							
7:30							
8:00							
8:30							
9:00							
9:30							
10:00							
10:30							
11:00 PM							
11:30							

1

4

2

2

37.8 RETURNING ACTIGRAPH TO KIDMAC

37.8.1 Participants Returning ActiGraph directly to KIDMAC

When an ActiGraph is shipped to a clinical site, KIDMAC will provide a pre-filled airbill, packaging and “Study Site Instructions” sheet to return the device after the participant’s use. **The study coordinator should instruct the participant to return the ActiGraph to KIDMAC on the 8th day and give the participant the “ActiGraph Return Instructions” sheet**, which explains how to ship the ActiGraph to KIDMAC.

A pre-paid and pre-labeled FedEx shipping envelope will be given to the participant.

The return airbill will contain the following primary mailing address:

Lucy Mulqueen
KIDMAC
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, E7650
Baltimore, MD 21205

The return address will be the clinical site (both will be pre-filled by KIDMAC).

Participants will put the device in the Bubble Mailer and then the Bubble Mailer in the FedEx envelope; they can drop the envelope off at any FedEx store or call FedEx to pick it up at home. When scheduling a FedEx pickup, the family should call 1-800-463-3339 and ask to speak with a FedEx representative. Speaking with a FedEx representative ensures that the correct pick-up address is arranged with FedEx. **The family should NOT schedule pick-up using the automated system and package should not be left at a drop box.**

Sites should remind the family of the importance of returning the device in a timely fashion so that the device can be used by other participants. Also sites should contact the families a couple days after the participant’s recorded stop date to remind them to return the device. **Remember, timing is important!!**

After parent has confirmed the device has been shipped, the coordinator must go to the CKiD website and complete the “On-line Shipping Form” located on the Coordinator’s Corner. Completing the “On-line Shipping Form” alerts KIDMAC that a device is being sent back.

37.8.2 Clinical Sites Returning ActiGraph to KIDMAC

Clinical sites should strongly encourage participants to return their ActiGraph directly to KIDMAC using FedEx. However, if it is more convenient for the participant to return the device to the site, they may do so. The site should follow the shipping instructions to ship the device back to KIDMAC.

37.9 QUESTIONS AND CONTACTS

If you have any questions regarding the process for requesting and/shipping monitors to KIDMAC or need further information, please use the following contact information below.

Lynn Pereira
KIDMAC

E-mail: lpereira@jhu.edu

Phone: 410-502-2755

Jackie Ndirangu
Project Director
East Coast Clinical Coordinating Center

E-mail: NdiranguJ@email.chop.edu

Phone: 267-425-1392

Julie Starr
Project Director
Midwest Clinical Coordinating Center

E-mail: jwstarr@cmh.edu

Phone: 816-302-3309

Actigraph Diary

Study ID # |_| - |_|_| - |_|_|_|
 CKiD VISIT #: _ _ _
 MONITOR #: _ _ _ _

Thank you for agreeing to wear the Actigraph physical activity monitoring device. During the visit, your CKiD study coordinator will place the Actigraph on your non-dominant wrist to make sure it fits comfortably with no problems. After the visit, if you have questions or concerns about the device please contact your clinical site coordinator.

Please follow the instructions:

1. Please wear the Actigraph device (as shown in photo) at all times for the next eight (8) days (**see date listed in step #3**).



If you plan to swim, you should remove the device during that time. Immediately after you finish swimming, put it back on. (Showering and short baths are ok).

2. If you must temporarily remove it for any reason (including swimming, sports activity etc.), please complete the table below. An example is provided.
 - Write the date and time the device was removed from your wrist.
 - Write the date and time when the device was put back on your wrist.

Date	Time Removed	Time Replaced	Reason for removal
M M / D D / Y Y M M / D D / Y Y	____ : ____ AM / PM	____ : ____ AM / PM	(e.g. Swimming lesson)
M M / D D / Y Y M M / D D / Y Y	____ : ____ AM / PM	____ : ____ AM / PM	
M M / D D / Y Y M M / D D / Y Y	____ : ____ AM / PM	____ : ____ AM / PM	
M M / D D / Y Y M M / D D / Y Y	____ : ____ AM / PM	____ : ____ AM / PM	
M M / D D / Y Y M M / D D / Y Y	____ : ____ AM / PM	____ : ____ AM / PM	
M M / D D / Y Y M M / D D / Y Y	____ : ____ AM / PM	____ : ____ AM / PM	

3. On the last day, when the device face has a STOP hand on it, you should take off the device and put it back in the package you received from your clinical site. You should wear the device until:

Date and time: ____ / ____ / ____ : ____
 M M D D Y Y Y Y Please remove device when you wake up



4. Please note the exact day and time you removed the device:

Date and time: ____ / ____ / ____ : ____ AM/PM
 M M D D Y Y Y Y

5. To return the device, follow the shipping instructions.

Date	Time Removed	Time Replaced	Reason for removal
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	
___ ___ / ___ ___ / ___ ___ M M D D Y Y	___ : ___ AM / PM	___ : ___ AM / PM	

Please specify when activities occur outside of the school or work day during the week and how physically active you would rate each activity (please draw boxes for when each activity occurs and write in the level of activity). Examples of activities include watching TV, going to movies, sports, dance, church, work (if primarily a student), or playing/socializing with friends. See example schedule on last page. **Helpful tip: Record activities as they happen or at the end of each day to make filling out the calendar easier!**

Activity Codes:	1 = Sedentary	3 = Moderately active
	(e.g., sitting/reading)	(e.g. lots of walking)
	2 = Minimally active	4 = Highly active
	(e.g. some walking)	(e.g., sweating, heavy breathing)

Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
6:00 AM							
6:30							
7:00							
7:30							
8:00 AM							
8:30							
9:00							
9:30							
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8:00							
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10:30							
11:00 PM							
11:30							

Example of how to recording activities during the week.

Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
6:00 AM							
6:30							
7:00							
7:30							
8:00 AM							
8:30							
9:00							
9:30							
10:00	1						
10:30							
11:00							
11:30							
12:00 PM							
12:30							
1:00 PM							4
1:30							
2:00							
2:30							
3:00							
3:30							
4:00							
4:30							
5:00 PM							
5:30							
6:00		2		2			
6:30							
7:00							
7:30							
8:00							
8:30							
9:00							
9:30							
10:00							
10:30							
11:00 PM							
11:30							



Date:

RE: ActiGraph Physical Activity Device

DOB: _____

To Whom It May Concern:

_____ is currently wearing an ActiGraph Physical Activity device. The device is worn on the wrist and should be worn at all times. She/he may participate in her/his usual activities (including gym class or sports practice) while wearing the device.

Please feel free to contact us if you have any questions about this matter.

Sincerely yours,

Division of Pediatric Nephrology

ACTIGRAPH RETURN INSTRUCTIONS

PLEASE READ CAREFULLY!

DO NOT THROW AWAY SHIPPING MATERIALS

You need them to return the Actigraph to CKiD.

For PARTICIPANTS returning an Actigraph:

A prepaid & pre-labeled FedEx shipping envelope is included in your shipper. Save this FedEx envelope to use when returning the device to CKiD. When you are ready to return the Actigraph, follow these steps:

1. Place Actigraph device inside the Bubble Mailer.
2. Place Bubble Mailer in FedEx envelope. Seal envelope tightly.

3. Option 1: Place FedEx envelope **INSIDE** of FedEx Drop Box.
PLEASE DO NOT LEAVE PACKAGE OUTSIDE OF DROP BOX!

Option 2: Schedule FedEx courier pickup.

Call **1-800-463-3339** and schedule a courier pickup.

To ensure courier pickup from the correct location, please speak with a FedEx representative to arrange pick-up.

DO NOT schedule pick-up using the automated system.

4. Call study site once package is picked up by courier:

Site Coordinator: _____

Site Phone Number: (_____) _____

Please call study site if you have any questions.

For SITES returning an Actigraph:

It is preferred that the participant returns the device; however, if it is more convenient for the participant, the device can be given back to the site to return. The site should follow similar shipping instructions:

- 1. Place Actigraph device inside the Bubble Mailer.**
- 2. Place Bubble Mailer in FedEx envelope. Seal envelope tightly.**

**3. Option 1: Place FedEx envelope INSIDE of FedEx Drop Box.
PLEASE DO NOT LEAVE PACKAGE OUTSIDE OF DROP BOX!**

Option 2: Schedule FedEx courier pickup.

Call 1-800-463-3339 and schedule a courier pickup.

To ensure courier pickup from the correct location, please speak with a FedEx representative to arrange pick-up.

DO NOT schedule pick-up using the automated system.

- 4. Complete the CKiD online shipping form to notify KIDMAC that the device was shipped back.**

DECLARATION OF CONFORMITY

IN ACCORDANCE TO ISO/IEC GUIDE 22

FOR

Activity Monitors

- MANUFACTURER:** ActiGraph
49 East Chase Street
Pensacola, Florida 32502
Phone: (850) 332-7900 Fax: (850) 332-7904
- MODEL NUMBER:** GT9X
- REPORT #:** F2LQ6006A-05E, F2LQ6006A-04E, F2LQ6006A-03A
- DIRECTIVES:** **Medical Devices Directive 93/42/EEC**
RTTE Directive (1999/5/EC)
- STANDARDS:**
- *EN 60601-1-2:2007, inc. C:2010 Medical Electrical Equipment Part 1-2: General Requirements for Basic Safety and Essential Performance – Collateral Standard: Electromagnetic Compatibility – Requirements and Tests*
 - *EN 61000-4-2:2009 Electromagnetic Compatibility-Part 4: Testing and Measurement Techniques – Section 2: Electrostatic Discharge Immunity Test*
 - *EN 61000-4-3:2006, inc. A2:2010 Electromagnetic Compatibility-Part 4: Testing and Measurement Techniques – Section 3: Radiated, Radio-Frequency, Electromagnetic Field Immunity Test*
 - *EN 61000-4-4:2004, inc. A1:2010 Electromagnetic Compatibility – Part 4: Testing and Measurement Techniques – Section 4: Electrical Fast Transient/Burst Immunity Test*
 - *EN 61000-4-5:2006 Electromagnetic Compatibility – Part 4: Testing and Measurement Techniques – Section 5: Surge Immunity Test*
 - *EN 61000-4-6:2009 Electromagnetic Compatibility – Part 4: Testing and Measurement Techniques – Section 6: Conducted Immunity Test*
 - *EN 61000-4-8:2010 Electromagnetic Compatibility-Part 4: Testing and measurement techniques – Section 8: Power frequency magnetic field immunity test*
 - *EN 55022:2006 inc A1:2007 Information Technology Equipment – Radio Disturbance Characteristics – Limit and Methods of Measurement*
 - *EN 300 489-1 V1.9.2:2011 Electromagnetic Compatibility and Radio Spectrum Matters; EMC standard for radio equipment and services; Part 1: Common technical requirements*
 - *EN 301 489-3 V1.4.1:2002 Electromagnetic Compatibility and Radio Spectrum Matters; EMC standard for radio equipment and services; Part 3 Specific conditions for Short-Range Devices (SRD) operating on frequencies between 9 kHz and 40 GHz*
 - *EN 300 328-2 V1.8.1:2012 Electromagnetic compatibility and Radio Spectrum Matters; Wideband Transmission Systems; Data transmission equipment operating in the 2,4 GHz ISM band and using spread spectrum modulation techniques; Part 2: Harmonized EN covering essential requirements under article 3.2 of the R&TTE Directive*
 - *EN 55016-2-3:2010 Specification for radio disturbance and immunity measuring apparatus and methods. Methods of measurement of disturbances and immunity. Radiated disturbance measurements*

**TESTING
FACILITIES:**

*F-Squared Laboratories
26501 Ridge Road
Damascus, Maryland 20745*

*F-Squared Laboratories
16740 Peters Road
Middlefield, Ohio 44062*

*CKC Laboratories, Inc.
5046 Sierra Pines Drive
Mariposa, CA 95338*

The Activity Monitor, *GT9X*, is in effective conformance to the Directives and Standards referenced above.

Authorized by:



Date: December 3, 2014

Name: Adam T. Simon

Title: Quality/Regulatory Manager



Quick Start Guide

ActiGraph GT9X Link + ActiLife

Activity Monitor: ActiGraph GT9X Link | Revision: A | Released: 11/24/2014



Quick Start Guide

ActiGraph GT9X Link + ActiLife



Activity Monitor: ActiGraph GT9X Link | Revision: A | Released: 11/24/2014

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Overview



ActiGraph GT9X Link

The ActiGraph GT9X Link is the most sophisticated activity monitor available from the global leader in actigraphy measurement. The ActiGraph Link combines our extensively validated accelerometry measurement technology with a variety of advanced new features, including:

Bluetooth® LE

Enables wireless device features (heart rate monitoring, proximity detection) and communication with ActiGraph mobile applications.

Programmable display

An LCD window displays date and time, provides optional real-time subject feedback, or can be completely disabled.

Specifications

Dimensions	3.5 x 3.5 x 1 cm	Dynamic range (primary accelerometer)	+/- 8G	Water resistance	1 meter, 30 min.
Weight	14 grams	Dynamic range (secondary accelerometer)	+/- 16G	Wear location	Wrist, waist
Sample rate	30-100 Hertz	Gyroscope dynamic range	+/- 2000 deg/sec	Warranty	1 year
Battery life	14 days*	Magnetometer dynamic range	+/- 4800 micro-Tesla		
Data storage	240 days/4 GB	Communication	USB, Bluetooth® LE		

* Rechargeable Lithium Ion, wireless and gyro disabled, 30 Hz sample rate

Wear time sensor

Automatically detects if a wrist worn device has been removed for simplified compliance monitoring and data cleaning.

Inertial Measurement Unit (IMU)

Contains a secondary accelerometer and gyroscope and magnetometer sensors to capture position and rotation data for advanced applications.

This Quickstart Guide provides instructions on how to setup, deploy, and download data from the ActiGraph Link with the ActiLife software.

What You'll Need



ActiGraph Link



ActiLife software (version 6.11.5 or higher)



Single Dock



Six Port Link Dock (Optional)



Link Wrist Band

Or



Link Belt Clip

Or



Pouch with Belt Loop



USB Cable(s)



Waist Belt (Optional)



Heart Rate Monitor (Optional)

1

Install ActiLife software

You must be running ActiLife version 6.11.5 or higher to operate the ActiGraph Link device.

- 1 Go to <http://www.actigraphcorp.com/product-category/software> and click the 'Download' button. Follow the prompts to install the ActiLife software on your PC.
- 2 When prompted, enter the ActiLife license key that was provided at the time of purchase to complete the installation.

View ActiLife System Requirements

Note: The ActiLife full version and ActiLife Lite can both be used to initialize and download data from the ActiGraph Link. However, the ActiLife full version is required to view and/or process the collected data.



2

Charge the battery

ActiGraph Link devices contain a rechargeable battery that should be fully charged before initialization and deployment to subjects. ActiLife will not initialize a device if the battery has dropped below a certain level. It takes approximately three hours to charge a fully depleted battery.

- 1 Connect the Link dock to the computer or a wall outlet using the mini USB cable.
- 2 Plug the ActiGraph Link into the dock with the ActiGraph logo facing up. Once connected, the red LED light on the right side of the dock will turn yellow, the device screen will display the serial number, and the battery icon will blink to indicate charging.
- 3 Once the device is fully charged, the yellow light will turn green and the battery icon on the device will show as full and stay on steady.



Charging multiple devices

To charge multiple ActiGraph Link devices simultaneously, plug up to six devices into the six port Link dock and connect to the PC and a wall power outlet using the supplied cables. The corresponding indicator light on the dock will turn green once each device is fully charged.

Note: ActiLife software is not required for battery charging.

Note: Battery voltage can be checked by opening the ActiLife software, connecting the device, and viewing the 'Battery' column in the grid under the 'Devices' tab. Select 'Refresh' to update the voltage level during charging.

Battery
3.44V (5% Normal)

Battery life specifications

The ActiGraph Link has several features that impact battery life when enabled. Estimated battery life for common device configurations are as follows:

Display On, Wireless/Heart Rate Off, IMU Off: 14 days

Display On, Heart Rate On, IMU Off: 7 days

Display On, Wireless/Heart Rate Off, IMU On (all sensors): 1 day

* Default sample rate of 30 Hz, raw data collection mode, idle sleep modes

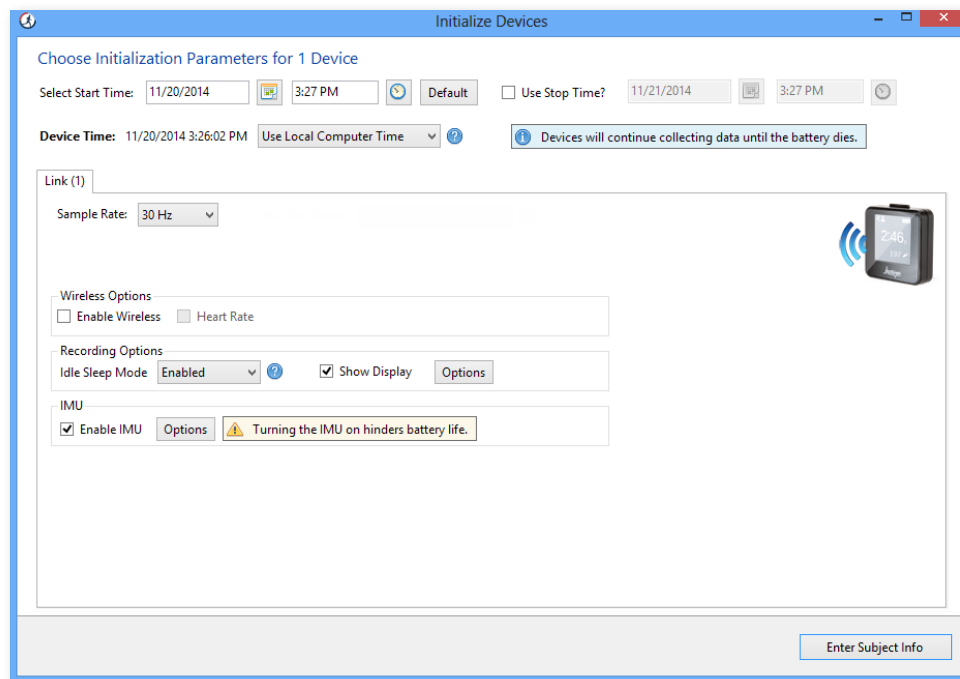
Note: These estimates are based on average device usage parameters. More frequent use of wireless communication will result in reduced battery life.



Device Charging Indicator Light

Setup and Initialization

- 1 Open the ActiLife software.
- 2 Connect the ActiGraph Link to the PC using the Link dock. The monitor will appear in the grid under the 'Devices' tab.
- 3 Select 'Initialize'. A submenu will open to display several initialization options.
- 4 Select 'Regular Initialization' from the submenu. A dialog box will open to display the initialization parameters listed below. The most commonly used initialization parameters are pre-selected as system defaults.



- **Start and Stop Times**

Enter the dates and times when the device should start and stop collecting data. If no start time is selected, the system defaults to two minutes ahead. If no stop time is selected, the device will continue to collect data until the battery is depleted, the memory capacity is full, or it is downloaded and reinitialized.

- **Device Time**

Set device to local computer time or atomic time.

- **Sample Rate**

Select the device sampling rate ranging from 30 to 100 Hz. Note that higher sampling rates will result in reduced device storage capacity and battery life.

Setup and Initialization (Continued)

- 6 Enter subject name, biometric information, and wear position details into the grid. Note that a subject name is required for initialization, but other biometric and wear details can be entered during download or data analysis.
- 7 Select **'Initialize 1 Device'**. A progress bar in the devices grid will indicate when the initialization process is completed.
- 8 After initialization is complete, remove the ActiGraph Link from the dock. Once removed, a 10 second wear sensor calibration countdown will begin. For wrist worn devices, immediately insert device into watch band (see Wearing the ActiGraph Link below) and lay it down on a flat surface until the countdown is complete. This calibration procedure is not required for waist worn devices, which do not provide valid wear sensor data.
- 9 The device will begin collecting data when the selected start time elapses, as indicated by the active mode icon in the upper left corner of the display. The device will continue to collect data until the stop time occurs (if selected), the battery is depleted, or the device is downloaded and reinitialized.

Note: If the start time elapses before the initialization process is complete, an error message will appear. Simply select the 'Default' button in the Start Time section to reset the default start time and then select 'Initialize 1 Device'.

Note: Multiple devices can be initialized simultaneously using the six port Link dock and/or multiple single Link docks. In this case, all devices will be programmed with the same initialization parameters and the Subject Info grid will display serial numbers of all connected devices for assignment.

Deployment & Information for Subjects

1

ActiGraph Link Screen Icons



Active Mode
Device is collecting data.



Heart Rate Not Connected
Device is configured to collect heart rate, but is not connected to a heart rate monitor.



Battery
Battery level in 20% increments. Icon cycles during charging.



Mobile Connect
Device is communicating with mobile app via Bluetooth®.



Battery Warn
Battery has reached critically low level. Estimated remaining charge (%) is displayed.



Reset Mode
Device is in a low power state.



Delay Mode
Device has been initialized but start time has not yet elapsed.



Steps
Shows steps accumulated for current day (12:00:00am - 11:59:59pm).



Halt
Device is in halt mode and not collecting data. Either the stop time has elapsed or the battery was fully depleted and recharged.



Wireless Broadcaster
Wireless is enabled.



Heart Rate Connected
Device is collecting HR data. Beats per minute (BPM) will appear if display is enabled.

2

Wearing the ActiGraph Link

The ActiGraph Link will typically be worn at the waist or on the non-dominant wrist. The appropriate wear location is dependent on specific research objectives and will be outlined in the study protocol.

Note: The device must be worn at the wrist location to obtain accurate readings from the wear time sensor.

Note: The device must be worn at the wrist location to obtain accurate sleep score information.

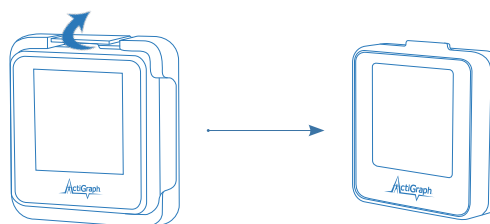


Wrist worn devices

Insert the ActiGraph Link into the wrist strap by positioning the plastic notch on the bottom edge of the device into the matching groove in the bottom edge of the watchband. Ensure that the ActiGraph logo on the device and the 'A' on the watchband are facing in the same direction. Gently push down on the upper portion of the device until it snaps into place.

The subject should be instructed to wear the device strapped securely to the non-dominant wrist with the logo facing up when viewed like a wrist watch.

To remove the ActiGraph Link from the watchband, firmly grasp and pull up on the device with one hand while gently lifting the plastic tab on the top edge of the watchband with the other hand.



Waist worn devices

Belt Clip

Insert the ActiGraph Link into the belt clip by positioning the plastic notch on the bottom edge of the device into the matching groove on the bottom edge of the belt clip. Ensure that the ActiGraph logo faces up when the clip opening faces down. Clip the device to the elastic waist belt or the subjects' own belt or waistband. The belt should be fastened securely against the subject so the device is snug against the body.

To remove the ActiGraph Link from the belt clip, firmly grasp and pull up on the device with one hand while gently lifting the plastic tab on the top edge of the belt clip with the other hand.

Deployment & Information for Subjects (Continued)



Pouch with Belt

Insert the ActiGraph Link into the belt pouch and secure flap using velcro tab. Thread an elastic waist belt or the subject's own belt through the loop on the back of the pouch. The belt should be fastened securely against the subject so the device is snug against the body.



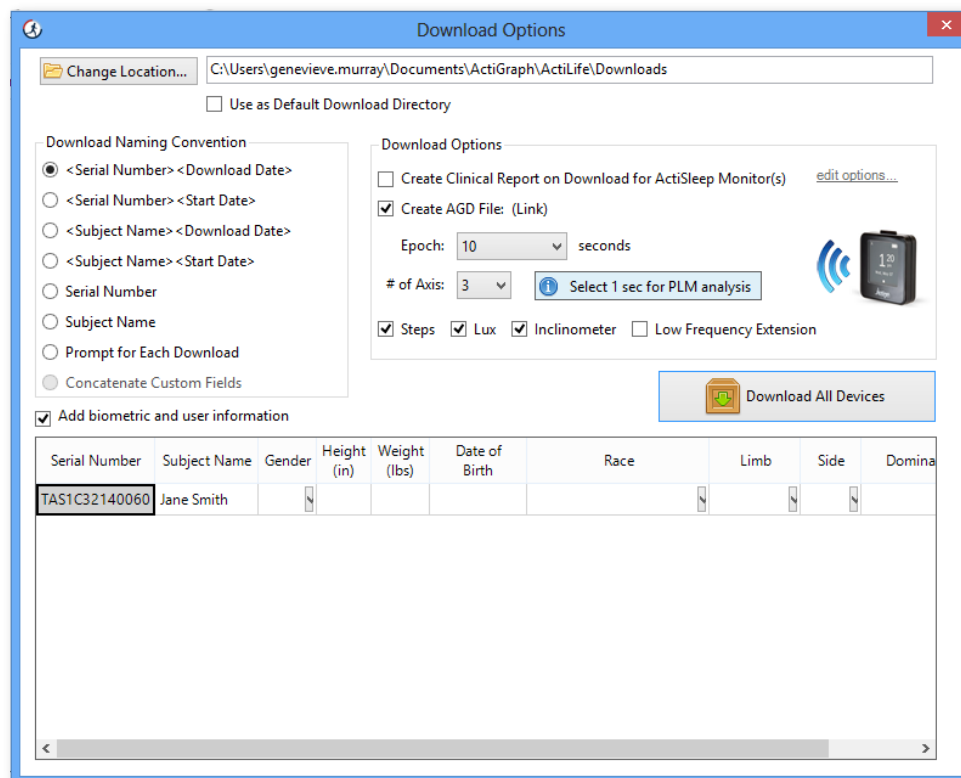
Heart Rate Monitor

To collect heart rate information, the **'Heart Rate'** option must be enabled during initialization and a compatible Bluetooth® wireless heart rate monitor is required. Unsnap the heart rate transmitter from the chest strap, position the transmitter in the center of the sternum, and snap back into place. Adjust the strap so that it is secure across the breast bone.

The ActiGraph Link will automatically begin collecting heart rate information when in range of the chest strap, as indicated by the heart rate screen icon on the device.

Downloading the Data

- 1 Open the ActiLife software.
- 2 Connect the ActiGraph Link to the PC using the dock station. The monitor will appear in the grid under the 'Devices' tab.
- 3 Verify the box in front of the device is checked and select 'Download' from the taskbar menu.
- 4 A dialog box will open to display the download options listed below. The most commonly used download parameters are preselected as defaults.



- a File download location
Select where downloaded files will be saved.
- b Download naming convention
Provides a list of file name formats.
- c Download Options:
 - Create Clinical Report
A customizable PDF report containing summary data will be automatically generated on download. Subject measures and scoring algorithms can be selected by clicking 'edit options'.

Downloading the Data (Continued)

- **Create AGD File**

An AGD file, required for data scoring, will be automatically created on download.

- **Epoch:** Select the desired epoch length for the AGD file.
- **# of Axis:** Select which axes of data should be included in AGD file.

Note: Axis 1=Y; Axis 2=X,Y; Axis 3=X,Y,Z

- **Steps:** Select to include step count data in AGD file.
- **Inclinometer:** Select to include positional data in AGD file.
- **Low Frequency Extension:** Select to apply low frequency filter extension to AGD file.

Note: The Low Frequency Extension option should only be used in very specific use cases where physical activity is at such a low level that it might otherwise be eliminated with our normal filter. An example would be very slow shuffling movements, common in elderly populations.

- d **Biometric and User Information**

Subject biometric information can be entered and/or edited. Fields will be pre-populated if this information was entered during initialization.

- 5 Once Download Options are selected, click '**Download All Devices**'. The dialog box will close and a progress bar will appear under the '**Status**' column in the grid.
- 6 When the download is complete, a '**finished downloading**' link will appear. Click this link to reveal options to view data, export the raw data file, and navigate to the download folder.
- 7 Data has now successfully been downloaded from the ActiGraph Link and can be cleaned and scored using the analysis tools in ActiLife.

Note: Collected data will remain on the ActiGraph Link device until it is reinitialized.

Viewing the IMU Data

- 1 After completing the download, select **File > Import/Export/Convert > IMU** in the ActiLife task bar.
- 2 Select the raw (.gt3x) file from the list and click 'Open.'
- 3 A status bar will appear while ActiLife converts the raw file to CSV. Once completed, the file location window will open and the IMU file will appear in the list.

About the IMU file

The IMU file will contain some or all of the following information based on the IMU selections made during initialization. The sample rate of the IMU file is fixed at 100 Hz.

Timestamp	Accelerome	Acceleromet	Accelerometer	Temperature	Gyroscope X	Gyroscope Y	Gyroscope Z	Magnetometer X	Magnetomete	Magnetom
2014-11-04T09:25:59.0000000	0.418945	-0.60791	0.327637	63.016354	69.763188	-28.564455	13.977052	27.246092	9.667968	15.234374
2014-11-04T09:25:59.0100000	0.441406	-0.554688	0.32666	63.726211	51.635745	-48.828128	9.216309	27.246092	9.667968	15.234374
2014-11-04T09:25:59.0200000	0.475586	-0.530273	0.333496	63.78312	34.790041	-74.157719	3.90625	27.246092	9.667968	15.234374
2014-11-04T09:25:59.0300000	0.48584	-0.477539	0.293945	63.768144	31.127932	-94.421392	-2.624512	27.246092	9.667968	15.234374
2014-11-04T09:25:59.0400000	0.439453	-0.373535	0.26709	63.768144	33.447268	-97.10694	-11.413575	27.246092	9.667968	15.234374
2014-11-04T09:25:59.0500000	0.289551	-0.293945	0.527344	63.759158	49.56055	-54.382328	-16.967774	27.246092	9.667968	15.234374
2014-11-04T09:25:59.0600000	0.225098	-0.227539	0.425781	63.753168	83.190923	-15.502931	-2.685547	27.246092	9.667968	15.234374
2014-11-04T09:25:59.0700000	0.270996	-0.169922	0.38623	63.768144	102.050787	-10.864258	21.240236	27.246092	9.667968	15.234374
2014-11-04T09:25:59.0800000	0.330566	-0.135254	0.400879	63.759158	114.807136	1.831055	39.489749	27.246092	9.667968	15.234374

Timestamp

- The timestamps shown in the exported .csv file are formatted to show the full date in YYYY-MM-DD format. The "T" symbol indicates the beginning of the time element for the timestamp. The time is formatted as hh:mm:ss.ss where the last "ss" represents the fractional portion of the timestamp. Each entry increments by 0.01 seconds (because of the 100Hz fixed sample rate)

Accelerometer X, Y, Z

- Each accelerometer entry represents instantaneous acceleration for the axis indicated in units of gravity (Gs). Device orientation is shown [in this help](#) article.
- The accelerometer on the IMU has a dynamic range of +/- 16Gs per axis

Gyroscope X, Y, Z

- Gyroscope measurements from the IMU represent are presented in degrees/sec for each axis. Refer to [this help article](#) for details regarding roll/pitch/yaw orientation.

Magnetometer X, Y, Z

- The IMU magnetometer readings represent the magnetic field experienced by the Link device and are useful for discerning directional orientation (compass). These readings are in microTesla (μT)

IMU Temperature

- The IMU temperature reading indicates ambient temperature inside of the Link activity monitor and is indicated in degrees Celsius (C).

Note: The accelerometer data in the IMU file is not from the primary accelerometer and is not used for scoring in ActiLife.

Frequently Asked Questions

Q Is the ActiGraph Link waterproof?

The ActiGraph Link is water resistant to 1 meter for 30 minutes according to IP27 certification. The device can be worn during bathing and swimming activities.

Q How should I clean the ActiGraph Link and accessories after use by a subject?

The ActiGraph Link, wristband, and belt clip should be wiped down using any alcohol based solution. Elastic belts and pouches should be laundered.

Q Is the raw accelerometer output the same as with ActiGraph's previous devices?

Yes, the ActiGraph Link uses the same accelerometer and sampling and filtering methods as the GT3X+ line of activity monitors.

Q Is there any way for the subject to change or reprogram the ActiGraph Link display after it has been deployed?

No, the ActiGraph Link display will operate according to the parameters selected during initialization until it has been reinitialized with ActiLife.

Q Does the wear sensor work at the waist?

No, the wear sensor is only accurate for wrist worn devices.

Q What do the various sensors in the IMU measure?

The accelerometer measures acceleration normalized to Earth gravity (g). The gyroscope measures angular rates in degrees per second. The magnetometer measure magnetic field strength in microteslas. The thermometer measures temperature of the IMU in Celsius.

Q Does the magnetometer provide accurate measurements in any geographic location?

Variations in magnetic north versus true north vary by location in a predictable way. There are lookup tables available. The magnetic field measurements may also be affected by hard and soft iron effects.

Q Can I calculate body temperature using the thermometer in the IMU?

No, the thermometer measures the temperature of the the IMU sensor for possible compensation of the IMU output.

Contact Us

Please contact our Customer Support Team with any questions or for additional information about operating the ActiGraph GT9X Link.

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