1. Introduction

ACKNOWLEDGEMENT

The Investigators and authors of this manual would like to thank the MESA Study and the AASK Study Group for permission to adapt their study materials for use in this manual.

1.A. CRIC Overview

The Chronic Renal Insufficiency Cohort (CRIC) Study is a landmark research project that strives to provide greater insight into the epidemiology of chronic renal insufficiency (CRI). It will focus research activities on the prediction and mechanisms of progressive renal disease and cardiovascular events among a diverse sample of adults with CRI.

1.A.1. Objectives

The overarching aim of the Chronic Renal Insufficiency Cohort (CRIC) Study is to establish a collaborative CRI research group capable of examining hypotheses concerning disease etiology, diagnosis, health outcomes, and health services utilization among a cohort of participants with CRI.

1.A.2. Description

Each of the seven participating clinical centers will plan to enroll approximately 430-500 participants using a recruit with replacement approach, to establish the baseline cohort of 3000 CRIC participants.

The CRIC Study population will include a racially and ethnically diverse group of adult patients (age 21 – 74) with mild-to-moderate CRI, approximately half of whom will have diagnosed diabetes mellitus (DM). Principles underlying the targeted composition of the cohort are:

- adequate representation of target subgroups (e.g. DM, women)
- subgroup analysis
- sufficient representation of subgroup to enable selection of a subcohort capable of addressing needs for developing CRIC GFR estimating equation

1.B. Study Organization

Participants will be recruited from the following seven Clinical Centers and their associated clinical sites as listed in the table below.

1.B.1. Clinical Centers (CC) and Sites

NAME	LOCATION
University of Pennsylvania Medical Center	Philadelphia, PA
Johns Hopkins Medical Institutions	Baltimore, MD
University of Maryland	
Case Western Reserve University	Cleveland, OH
University Hospitals of Cleveland	
Metrohealth Medical Center	
Cleveland Clinical Foundation	
University of Michigan at Ann Arbor	Ann Arbor, MI
St. Johns Health System	
Wayne State University/Detroit Medical Center	
University of Illinois at Chicago	Chicago, IL
Tulane University Health Science Center	New Orleans, LA
Kaiser Permanente of Northern California	Oakland, CA
University of California, San Francisco	

1.B.2. Participating Laboratories and Reading Centers

CENTRAL READING CENTER	*PRINICIPAL INVESTIGATOR*
Central GFR Laboratory ..... Cleveland Clinic Foundation, Cleveland, OH	Phillip Hall, M.D.
Centralized Biochemistry Laboratory ..... University of Pennsylvania, Philadelphia, PA	Daniel Rader, M.D. Consultant: Paul Ridker, M.D.
EBT ..... Los Angeles County Harbor-UCLA Medical Center, Torrance, CA	Matthew Jay Budoff, M.D., F.A.C.C
ECG .... Wake Forest University School of Medicine, Winston Salem, NC	Ronald J. Prineas, M.D., Ph.D.
Echocardiography..... University of Pennsylvania, Philadelphia, PA	Martin St. John Sutton, M.B.B.S.

1.B.3. Scientific and Data Coordinating Center

University of Pennsylvania School of Medicine
Center for Clinical Epidemiology and Biostatistics
Philadelphia, PA

Principal Investigator:	Harold I. Feldman, M.D., M.S.C.E.
Co-Principal Investigator:	J. Richard Landis, Ph.D.
Co-Investigators:	Cheryl Anderson, Ph.D.
	Marshall Joffe, M.D., Ph.D. M.P.H.
	Stephen E. Kimmel, M.D.
	Shiriki Kumanyika, Ph.D., M.P.H.
	Daniel J. Rader, M.D.
	J. Sanford Schwartz, M.D.

1.B.4. Funding

Funding for CRIC is provided by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), a division of the National Institutes of Health (NIH), Department of Health and Human Services.

1.B.5. Project Cycle

The entire CRIC project will span eight years. The first eighteen months of the study have been devoted to protocol development, staff training, and pilot testing. The recruitment phase of the study will occur over a 33-month period beginning in May 2003. This includes a screening and baseline visit, though these visits may be combined. Participants will be followed for up to six years depending on enrollment date. They will be contacted by telephone six months after an annual clinic visit. As such, enrollment and follow-up activities will occur simultaneously. The final months of the project will be dedicated to evaluation and data analysis for publication.

1.B.6. Sub-Cohort Selection

One third of participants will be selected to participate in additional subcohort studies. Participants selected for the subcohort will experience Iothalamate Glomerular Filtration Rate (GFR) and Electron Beam Tomography (EBT) tests. The rest of the cohort will not experience these tests. One thousand participants will be selected from among the entire cohort of CRIC participants. Initially this will occur randomly based on eligibility criteria for these studies. Evaluation of the subcohort relative to its representation of the entire cohort may alter this selection process.

1.C. General Policy

1.C.1. General Protocol Policy

The objectives of the trial are most likely to be achieved if the protocol does not require alteration. Any changes in the protocol will result in some degree of heterogeneity of the data, which complicates the analyses and may compromise the scientific integrity of the study. However, occasions may arise in which protocol changes are necessary. Therefore, changes in the protocol will be considered only if they are required to ensure participant safety or will significantly enhance the scientific validity of the study.

The Steering Committee must approve all protocol amendments or revisions. Amendments must be submitted to the IRB for approval and once approved, be incorporated into the protocol. IRB approval must occur prior to the implementation of an amendment. Amendments that include minor changes to the protocol may undergo expedited review if these changes fit into expedited approval criteria. All changes to the informed consent form must also be approved by the IRB.

1.C.2. Human Subjects Considerations

1.C.2.(a). Regulatory Requirements for Informed Consent

Each Clinical Site is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its local Institutional Review Board (IRB) and in accordance with the Common Rule (45 CFR Part 46 subpart A, Protection of Human Subjects). The informed consent form must be obtained (signed and dated by the participant) prior to initiation of any study related activity.

The Informed Consent form must provide the following information to each participant:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

1.C.2.(b). Administration of Informed Consent

Potential participants will be asked to sign two Informed Consent forms. The first consent form describes the Chronic Renal Insufficiency Cohort (CRIC) study; the second consent describes the optional Genetic Sample component of the study. Each of the forms contains embedded YES/NO questions and has its own signature requirements. Instruct the participant to read both Informed Consents carefully and to raise any questions or concerns that he/she has and to sign them ONLY after their questions or concerns have been answered. Participant questions should be answered using lay language.

Potential participants may be uneasy about providing their Social Security Numbers. Explain to them how the number will be used and that it will be stored in an encrypted fashion. **Participants must respond to this YES/NO question in the CRIC Study Informed Consent Form**.

Participants may decide to participate in the CRIC Study but opt out of all or parts of the genetic study. Discuss the options and implications of participation in the genetic study and explain the selections contained in the YES/NO questions about genetic samples. **Participants must respond to these YES/NO questions in the Genetic sampling Informed Consent Form**.

Responses to the YES/NO questions about provision of genetic samples and Social Security Number should be recorded in questions 18a and 18b of the Eligibility [ELIG] CRF.

Provide a copy of the signed form to the participant before they leave the clinical center and instruct the participant that they should feel free to contact the clinical center should further questions occur to them after the visit.

An informed consent *must* be obtained from the participant before study information is collected or study procedures performed.

1.C.3. Participant Confidentiality

1.C.3.(a). HIPAA

Participants must sign a Health Insurance Portability and Accountability Act (HIPAA) Authorization in addition to the two Informed Consent Forms. The HIPAA Authorization may or may not be incorporated into the CRIC Study consent depending on the policy of the Clinical Center. However, if the HIPAA language is incorporated into the Informed Consent Form, the regulation mandates that it be submitted to the IRB for prior approval. This form describes both the kinds of health information collected in this study and also all of the disclosures of health information that will be made. The form must also list parties to whom disclosures of personal health information will be made.

1.C.3.(b). Medical Record Release

This study may require the release of medical records from remote Health Care Facilities. Each Clinical Center must obtain written authorization for the release of medical records from each study participant. The following procedure is recommended:

- Obtain a copy of your Institution's Medical Release Form prior to study start.
- Assess whether the Institution's form addresses your study-specific needs, and if not, ask if it may be altered.
- Once finalized, insert a version date on the release form and make enough photocopies so that each participant enrolling in the study can receive three (3) copies.
- During The Informed Consent HIPAA Authorization process, ask each participant to sign and date three (3) copies of the Medical Release Form. Explain that these will be issued as needed to obtain data for the research study. (The release of medical records should be listed in the HIPAA authorization form that they should have previously signed.)
- Make a copy of the signed release form for your records. Remote Institutions may require the form with *original* signatures.
- Intermittently check with your Institution to see if the Medical Release Form has been revised.
- Each study participant should sign three (3) currently dated Medical Release Forms during their yearly site visit(s).

1.C.3.(c). Additional Confidentiality Concerns

- Do not record Social Security numbers without first ensuring that the study participant answered YES to this specific question on the Informed Consent Form.
- Social Security numbers will be stored in a scrambled fashion and will be unscrambled only to connect to other medical databases, such as Medicare.
- Only authorized study personnel may be permitted to view these social security numbers during use and they must be scrambled again immediately.
- Consent form(s), HIPAA authorizations and source documentation ***must*** be securely maintained in a separate location from the CRFs.
- Recruited study participants are assigned a *Participant ID* number, a unique study identification number.
- The SDCC staff has access to the *Participant ID* number for data management purposes. All communication between the DCC staff and the Clinical Center staff regarding participant data occurs via the *Participant ID* number only.

2. Participant Recruitment and Prescreening

2.A. Participant Recruitment

2.A.1. Overview of Recruitment

Each clinical center is committed to recruiting 430-500 participants into the CRIC Study. Recruitment sources and strategies will vary from center to center, but will most likely include computerized database searches, manual searches of medical records, referrals from health care providers, and patient panels of CRIC investigators. Investigators are encouraged to present the CRIC Study to their colleagues as well as to discuss it with other health care providers, particularly internists and nephrologists in the area. A patient brochure that describes the basic study objectives and information is available to aid in recruiting participants into the CRIC Study.

2.A.2. Recruitment Process

2.A.2.(a). Identifying potential participants

Each clinical center will identify potentially eligible participants via recruitment sources and strategies available at their particular center. These may include, but are not limited to, automated laboratory database searches of recently measured serum creatinine values that may indicate CRI, referrals from physicians or specialty centers (such as Diabetic or Nephrology Clinics) of potential participants who are known or suspected to have CRI, self referral from potential participants who may be responding to the study brochure, may read about the study in local newspapers or hear about the study from relatives or friends.

2.A.2.(b). Obtaining physician approval to contact potential participants

After identifying potential participants, each clinical center investigator will obtain permission to prescreen potential participants for the CRIC Study from the primary care provider (PCP). Each provider will be sent a mailing containing: (1) a letter asking for approval/refusal of participant contact, (2) a CRI information sheet, (3) a list of potentially eligible participants (4) business reply envelope, and (5) fax-back form. The objective is to clearly state why this will be a useful study to patients and to make is easy for PCP's to respond to the request to contact. Document the response to this request in your local tracking or filing system and file identifying information appropriately in a secure place.

PCP refuses contact: Enter this information into the local tracking system as MD refusal with the reason, if provided.

No response from PCP: If the PCP does not respond after one to two weeks, send a reminder by email or telephone. Decide upon the best approach to communicating with PCPs and send

additional reminders and messages. If after several attempts the PCP does not reply, send a message stating that direct contact with the patient is planned, if possible.

PCP approves contact: Enter this information into the local tracking system as MD approval.

Letters and email messages documenting this process will be filed in secure computers and/or cabinets at clinical centers and retained only as long as is necessary to determine potential participant's interest and eligibility in the CRIC Study.

2.B. Prescreening Visit (Visit 1)

2.B.1. Contacting potential participants

Once PCP approval has been obtained to contact the potential participant, he/she will be mailed a packet containing: (1) an introductory letter, (2) study brochure, and (3) reply card. The potential participant will be asked to return the reply card indicating whether or not they would like to be contacted.

- Participant refuses contact: Enter this information into the local tracking system as patient refusal with the reason, if provided. No further contact will be made.
- Participant approves contact: Begin contacting these participants by telephone as soon as possible.
- Participant does not reply after 3 weeks: Begin contacting these participants by phone.

If a potential participant agrees to discuss the study, contact them by phone as soon as possible, or as indicated on the reply regarding the best time to call. Maintain a telephone log of all attempted and actual contact with potential participants by phone, indicating the following information:

- Contact unsuccessful: If a potential participant is unreachable after several attempts at different times during the day, enter this information into the tracking system as unable to contact patient, with a brief explanation if possible.
- Contact successful: The potential participant has been contacted by phone. The prescreening script [SCRIPT1] will be read and the Prescreening Information [PRESCR] form completed.

2.B.2. Obstacles to reaching potential participants

1. Wrong or Disconnected numbers
    - If a phone number is wrong or disconnected, indicate this information in the tracking system.. Try to contact this patient again by mail.
2. Blocked/fast busy numbers
    - If a blocked number or a fast busy signal is reached, ask the operator to complete the call. The RC should tell the operator that he/she is having

difficulty with the number. Do NOT say that the number is blocked. Request that the operator complete the call. If asked, tell the operator to bill the call to the outgoing number.

3. When to call
   - If the potential participant cannot be reached, ask if there is a better time to call or another number where they may be reached.
4. How many times to call
   - Make several attempts to contact all participants. Try each number (day, evening, and message) at least twice during each of the following time periods (10:00 am - Noon, Noon - 6:00 pm, 6:00 pm - 8:30 pm, and anytime during the weekend) before leaving a message. If there is still no answer, leave a message such as the following:

> *Hello, my name is (----). I'm calling on behalf of CENTER NAME about an inquiry (he/she or you) made at our medical center. We would like to speak with (name of potential participant). Would you please call our toll-free number at NNN-NNN-NNNN and leave your name, your phone number with area code, and a good time to reach you. Thank you very much.*

Do not leave more than one message every couple of days. Do not leave repeated messages. Use your best judgment to ascertain if calls are being avoided or simply bad timing. If the potential participant still cannot be reached, file this information and plan to call again in a few weeks.

2.C. Pre-Screening Information

The goals of the telephone pre-screening are:

- To interest the potential participant to join the study.
- To confirm eligibility to participate in the study.
- To schedule the screening visit.

When the potential participant has been contacted by phone, read the Pre-screen Script [SCRIPT1] and/or Prescreening Exclusion Script [SCRIPT2].

- If the potential participant is willing and available to continue, complete the Pre - Screening [PRESCR] form with the potential participant.
- If the potential participant is willing, but unable to continue, ask permission to call back.
- If the potential participant is unwilling to continue, thank the potential participant for their time.

The RC should be familiar with the answers to the Frequently Asked Questions so that they are prepared to answer questions that the potential participant may have. If the RC does not know

the answer to a question, they should offer to find out the information and respond as soon as possible.

2.D. Quick Tips for Recruitment Calls

2.D.1. Language barriers

If the RC reaches a household that speaks a language in which they cannot communicate, indicate this information in the Comments section of the PRESCR form. If the appropriate study personnel are available and the potential participant is apparently eligible at this time, attempt to schedule them for a screening visit only if you are certain that the available clinical center staff can communicate in their language. Inform the center staff of language requirements.

2.D.2. Refusals

1. Occasionally a potential participant will be reluctant or refuse to be interviewed. Converting a refusal, or potential refusal, is a real skill. Find out what concerns the potential participant has about participating. Stress understanding of how he/she feels about not wanting to participate. The following phrases may be useful:
   - It is especially important to hear what you think.
   - We need the information that only you can give us.
   - Others may benefit from your experience.
   - Whatever you have to say is important for us to know and will help us learn more about your health and kidney disease.
   - If the potential participant is unhappy with his/her health plan: I can understand why you're upset. We are very interested in hearing what YOU have to say and in knowing how YOU feel.
2. Never coerce, intimidate, or threaten; it is better to lose an interview occasionally than risk creating or perpetuating ill will. Although it is possible to try to change the potential participant's mind, the wishes and privacy of anyone who does not want to be involved must be respected. Rather than lose an interview completely, offer to call back in a week or two. This will give the potential participant an opportunity to reconsider participating.
3. Do not try to persuade potential participants who are terminally ill, grieving the loss of a loved one, or otherwise emotionally unavailable for the interview. If the potential participant is willing, the interview may serve as a welcome diversion. If the potential participant is unwilling, or upset by the call, apologize for the untimely intrusion.

2.D.3. Respondents in a hurry to end a phone call

Sometimes a potential participant is in a hurry to get off the phone or wants to cut the interview short. This can be a problem with long interviews. If the interview is almost finished, let the potential participant know, and usually the participant will agree to finish. It helps to say "Just ___more questions" or "We'll be through in about _____minutes". If the interview is not almost finished, or if the potential participant becomes weary of the interview, say how much more time is needed to finish and let him/her decide whether to finish or reschedule another time to complete the interview. It is acceptable, though not preferred, to do an interview in two parts. Try to schedule a specific day and time to call back.

2.D.4. Respondents with hearing problems

If a potential participant has difficulty hearing a question, repeat it clearly and slowly without raising your voice. For some people, the louder the voice, the more distorted it sounds and the harder it is to hear, especially over the phone. A louder voice may convey the impression that the interviewer is impatient.

2.D.5. If the potential participant is deceased

If the potential participant has died, apologize for calling and express sympathy. "I'm sorry" or "I'm sorry to hear of your loss" is sufficient. If the household member is upset by your call, acknowledge how disturbing the call must be and apologize again for not being aware of the situation. Document this information and inform the project coordinator immediately, to insure that no further calls are made to this household.

3. CRIC Study Processes

3.A. Visit Schedule Information

This section of the manual provides a summary of activities and procedures that occur at each scheduled CRIC Study visit and contact. Specific directions for completing each Case Report Form [CRF] are found in Section 5 of this manual.

The table below describes the types of visits and permissible visit intervals (called visit window) used throughout this manual to describe interaction with CRIC Study participants. The participant study calendar, which is a tool available in the Data Management System (DMS), will be generated based on the date of the Baseline Clinic Visit [Visit #3]. All contacts and visits will have a permissible window of contact surrounding them that is minus and plus 2 months of the target date. For example: If the Visit #5 /12 Month target date is 12/01/2003, the annual clinic visit will not be considered out of range if it occurs between month 10 [10/01/2003] and month 14, 2/01/2004.

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
Pre-screening	Screening	Baseline	6 Mos	12 Mos	18 Mos	24 Mos	30 Mos	36 Mos	42 Mos	48 Mos	54 Mos	60 Mos
Phone or Clinic	Clinic Visit	Clinic Visit	Phone Contact	Clinic Visit	Phone Contact	Clinic Visit	Phone Contact	Clinic Visit	Phone Contact	Clinic Visit	Phone Contact	Clinic Visit

Several tools are available to assist you in organizing the required procedures, tests and forms associated with each visit and contact. Each CRIC Study visit has an accompanying checklist/progress note (eg PRESCRCL, SCRCL, BASECL), which lists processes for a particular clinic visit or telephone contact. In addition, the **Recruitment Chart [CHART1]** is a comprehensive list of the study processes that occur at Visits 1, 2 and 3. The **Follow-Up Chart [CHART2]** is a comprehensive list of the study processes that occur at Visit 4 through Visit 13.

3.B. Pre-Screening Contact [Visit # 1]

This contact may occur on the telephone or in person. The Research Coordinator (RC) will use the following forms to gather information during the Prescreening Contact:

Data Entry Forms:

- Prescreening Information [PRESCR]
- Prescreening Refusal [PREREF]

Administrative Forms:

- Health Data Review Form [HDREV]

- Prescreening Scripts [SCRIPT1] and [SCRIPT2]
- Data Processing Cover Sheet [DPCS]

The Prescreening process consists of several steps:

- The information collected from the medical record or other source is recorded on the Health Data Review [HDREV] form. It is expected that all information will not be available from the source of medical information. However, even partial completion of this form should assist the RC in determining whether a potential participant appears eligible or ineligible for the study.
- The HDREV form contains personal identifying information and is not entered in the study database. It is strictly a tool for gathering information so that the RC can assess and contact participants. It is not essential to answer all of the questions. Store these forms in a locked file cabinet.
- The HDREV form has a field for the estimated GFR (eGFR) value. This value can be calculated with a serum creatinine lab value using the tool that is available on the CRIC Study DMS. Note that this is not the value that is used to assess eligibility. It is simply available to you to assist in the information gathering stage of assessing eligibility. Instructions for using this tool are found in Section 7 of this manual.
- The RC will contact the primary health care provider of all participants who appear to be eligible to request permission to contact the participant and to discuss their potential participation in the CRIC Study.
- Participants will be contacted either by phone or in person by the RC to determine their interest and eligibility for the study. Permission to collect prescreening information is documented on the **Prescreening Scripts [SCRIPT1 or SCRIPT2]**; a form the RC will use to introduce the study.
- Once verbal consent is obtained, the RC will ask the participant the questions on the **Prescreening Information [PRESCR]** form. Based upon the responses, a determination is made by the RC regarding the participant's eligibility (ineligible or not ineligible), and their interest in participation (refused or not refused).
- If the RC is unable to make a determination of ineligible or not ineligible based on the information collected from the medical record and participant interview, the PI should be consulted and additional sources of information may need to be reviewed.
- Information gathered from other sources is stored in the source document folder, separate from the study binder.
- No further information will be collected about participants deemed ineligible. Participants deemed not ineligible but who refuse to participate in the study will be questioned regarding their decision and their response(s) will be recorded on the **Prescreening Refusal [PREREF]** form. Participants deemed not ineligible and who agree to participate will be scheduled for a screening visit and assigned a participant ID number.
- Participants should be scheduled for the Screening Visit (Visit 2) as soon as possible, though there are no restrictions or time limits to this interval.

3.B.1. Assignment of Participant ID

Participants who appear to be eligible following the Health Data Review [HDREV] will have their name recorded on the Participant ID Log [PTIDLOG] and will be assigned the next available participant ID number. Once a participant ID number has been assigned, it should never be reassigned for any reason. Participants assigned an ID number who are ineligible or refuse participation, and who later become eligible or decide to participate, should be assigned a new ID number. The **Participant ID Log [PTIDLOG]** should be stored in a secure, locked filing cabinet. The ID number will reflect the clinical center, site, and individual participant number.

There are seven primary clinical centers:

01 University of Pennsylvania

02 Johns Hopkins Medical Institutions

03 Case Western Reserve University

04 University of Michigan at Ann Arbor

05 University of Illinois at Chicago

06 Tulane University

07 Kaiser Permanente of Northern California

Some centers have satellite centers or referral centers that are also participating in the CRIC Study. These are referred to as 'sites' and are listed below:

3.B.2. Clinical Centers (CC) and Site Assignments

CC	Site	NAME	LOCATION
01	01	University of Pennsylvania Medical Center	Philadelphia, PA
02	01	The John Hopkins University	Baltimore, MD
02	02	***University of Maryland***	
03	01	Case Western Reserve University	Cleveland, OH
03	02	***University Hospitals of Cleveland***	
03	03	***Metrohealth Medical Center***	
03	04	***Cleveland Clinical Foundation***	
04	01	University of Michigan at Ann Arbor	Ann Arbor, MI
04	02	***St. Johns Health System***	
04	03	***Wayne State University***	
05	01	University of Illinois at Chicago	Chicago, IL
06	01	Tulane University Health Science Center	New Orleans, LA
07	01	Kaiser Permanente of Northern California	San Francisco, CA
07	02	***University of California, San Francisco***	

The eight digit participant ID is composed of 3 identifiers.

- The first two digits indicate the primary clinical center.
- The next two digits indicate the site.
- The final four digits are the sequential ordering of participants.
- Example: **ID# 02-02-0008** indicates the primary clinical center as the Johns Hopkins Medical Institutions, the site as the University of Maryland, the number is that of the eighth participant.
- Record all numbers, including leading zeroes, when you record this number on CRFs.

Participants assigned a CRIC ID # are considered prescreened and must be registered in the Data Management System. This step ensures that each CRIC ID number is a unique identification number.

3.C. Eligibility and Enrollment

Determining eligibility is a multiple step process involving the review of medical information, participant interview, and conference with the participant's healthcare provider and the PI. Information collected on the case report form Health Data Review [HDREV] form prior to or at the Pre-screening Visit represents the first step in determining a participants' eligibility based on available information.

3.C.1. Inclusion Criteria

Participants must sign and date the informed consent documents. Participants must be within the following age and estimated Glomerular Filtration Rate (eGFR) range to be eligible for the CRIC cohort. The eGFR value used to determine eligibility is calculated from the serum creatinine test drawn during the Screening Visit [Visit #2].

Age	eGFR (ml/min/1.73 m^2)
21 – 44 years	20 – 70
45 – 64 years	20 – 60
65 – 74 years	20 – 50

3.C.2. Exclusion Criteria

Based on self report, participants who meet any of the following exclusion criteria will not be eligible to participate in the CRIC Study:

- Institutionalized (e.g., prisoner, nursing home resident, skilled nursing facility resident)
- Unable or unwilling to provide informed consent
- Diagnosis of cirrhosis of the liver
- Diagnosis of polycystic kidney disease

- Diagnosis of cancer of the kidney
- Diagnosis of multiple myeloma
- Diagnosis of HIV infection or AIDS
- Diagnosis of chronic heart failure - experience symptoms of chronic heart failure with minimal physical activity or at rest
- Received immusuppressive drugs such as Cyclophosphamide, Cytoxan, Steroids, Prednisone, Cellcept, Cyclosporine for the treatment of kidney disease, within the past 6 months
- Received dialysis (peritoneal and/or hemodialysis) lasting more than one month
- Received a kidney transplant
- Received other organ or bone marrow transplants
- Received chemotherapy for cancer within the last 2 years
- Currently participating in the AASK Cohort study or KEEP study
- Currently participating in a clinical trial that involves intervention that may have an effect on renal or cardiovascular outcomes (as assessed by a Central Adjudication Committee)
- Based on the assessment of the investigator, study coordinator or designee, participant appears unlikely or unable to participate in the required study procedures

3.C.3. Additional Exclusion Criteria for Participants Undergoing ^{125}I-Iothalamate GFR Testing:

Participants who meet any of the following criteria will not be eligible to participate in the CRIC Study subcohort. These exclusion criteria do not prevent participants from participating in the main CRIC Study.

- Known iodine or shellfish allergy
- Currently breast feeding, or pregnant based on urine HCG test
- Has undergone any radionuclide diagnostic test other than those done with 99 Technetium or ^{125}I-Iothalamate GFR within the past 30 days (e.g.: thallium stress test)
- Require self-catheterization for voiding
- Impaired urinary voiding, defined by three or more of the following:
    - Awakening to urinate more than three times per night
    - Problems emptying the bladder
    - Incontinence/trouble holding urine
    - History of prostate problems
    - Urinary Tract Infection in the past year

NOTE: The determination of "impaired urinary voiding" is made by the PI or RC and is based on criteria listed above.

3.D. Screening Visit [Visit 2]

Activities and Procedures:

Informed consent process

Eligibility assessment

Blood draw [10 cc] and urine test

Blood pressure measurement

Urine Pregnancy test (for all women of childbearing age)

Instruction: Diet History Questionnaire [DHQ] and
24 Hour Urine Collection

Equipment:

Blood specimen supplies

Urine collection cup

Urine dipsticks

Urine Pregnancy test kit

24 hour urine collection kit

The Screening Visit consists of the following steps:

- Potential participants will sign and date written consent to participate prior to the conduct of any screening procedures. A copy of the signed informed consent will be given to the participant. The original signed consent form should be placed in the participant's study file. A second copy should be placed in a confidential study folder containing copies of consents for all study participants.
- The RC will further assess eligibility by interviewing the potential participant and recording the responses on the **Eligibility Assessment [ELIG]** form. Upon conclusion of the interview, the RC should be able to determine if the participant is a) eligible for the CRIC Study and b) eligible for the GFR subcohort. The RC should confer with the PI on questions related to urinary impairment and to make an overall decision regarding the participant's suitability for participation in the study.
- If the RC and PI are unable to make a determination of ineligible or not ineligible based on the information collected from the medical record and participant interviews thus far, additional sources of information may need to be reviewed. Any further Screening Visit activities should be deferred until a final determination can be made.
- Following the eligibility assessment, the RC will collect a blood sample and a urine sample. Fasting is not required prior to providing a blood sample, however; fasting status should be indicated on the **Screening Laboratory Results [SCRLAB]** form.

Record the institution lab code that indicates where the serum creatinine test was processed. The blood sample will be processed at the clinical center and a portion of the serum reserved for potential shipment to the CRIC Central Laboratory. The urine sample will be analyzed using a standard urine dipstick. All females of child-bearing potential will also have a urine pregnancy test.

- The participant will have their **Blood Pressure [BP]** measured following the protocol outlined in **Appendix A**. The RC will record the pulse and 3 sequential BP measurements while the participant is seated, followed by the pulse and one BP measurement while standing.
- The participant will be asked to complete the following administrative and data entered forms: **Demographic Information [DEMO], Participant Contact Information [PTCONT], and Health Provider Contact Information [HPCONT].** The RC should review these forms prior to the participant's departure to assess completeness. Participant Contact Information and Health Provider Contact Information should be reviewed and updated during each subsequent visit or phone contact.
- At the conclusion of the Screening Visit participants will be given a **Diet History Questionnaire [DHQ]** and the materials necessary for the collection of a 24-hour urine specimen along with instructions for completing the form and specimen collection. Instruct participants to take these materials home but not to complete the questionnaire or start the urine collection test until study eligibility has been confirmed. In most cases, the RC should be able to confirm eligibility and contact the participant within 48 - 72 hours.
- If the participant agrees to provide his/her Social Security Number (SSN), complete the **Encryption [ENCRP]** CRF.

3.E. Enrollment and Subcohort Selection

- The interval between the screening visit and the baseline visit is a maximum of 3 months. This allows the clinical sites an opportunity to confirm screening information, electronically enroll participant into the CRIC cohort and subcohort, and schedule the baseline visit to suit participants' preferences.
- To enroll a participant the following completed forms must first be entered and verified (double data entered) into the CRIC Study Data Management System (DMS):
    - **Eligibility Assessment [ELIG]**
    - **Demographics [DEMO]**
    - **Screening Laboratory Results [SCRLAB]**
    - **Blood Pressure [BP]**
- The eGFR module will calculate the participant's eGFR value using the age, gender, and race variables from the DEMO form, and the serum creatinine result from the SCRLAB form. The resulting value should be recorded on the **Participant Assignment [ASSIGN]** form.

- The Participant Assignment module will calculate a participant's eligibility for enrollment in the study based on 1) age and eGFR value, 2) eligibility assessment form. It will also indicate whether a participant has been assigned to the subcohort. Only 1/3 of participants will be selected for the subcohort.
- This process will take place within the Data Management System (DMS). The RC will select the menu option that opens the ASSIGN module.
- The module will require the RC to click on the eGFR calculate button and record the eGFR value on the ASSIGN form. The module will then assess eligibility and provide YES/NO responses to questions 2, 3 and 4 on the ASSIGN form, which the RC will record from the screen onto the form.
- The RC will then re-enter the values recorded for questions 2, 3 and 4 for confirmation purposes.
- Participants who are either not eligible for enrollment based on either 1) age and eGFR value, and/or 2) eligibility assessment, will require a **Participant Withdrawal [WITHDR]** form indicating "Participant ineligible at screening visit."
- The screening and baseline visits may be performed on the same day for participant convenience if the clinical center has the capability to process the screening serum creatinine value promptly and to have the above mentioned forms [ELIG, DEMO, and SCRLABS] double data entered. In the event of computer problems at either the clinical site or the SDCC, the combination of the screening and baseline visits may not be possible. The RC should contact the SDCC to determine if manual (not electronic) eligibility determination and enrollment are possible.

3.E.1. Baseline Registration

Prior to entry of the baseline data, the RC will be required to register the Baseline Visit date in the Data Management System. This serves as an official registration step after the Screening Visit [Visit #2], which includes eGFR calculation, eligibility determination, and subcohort selection]. Baseline visit registration is a key step in determining the follow-up visit schedule. This registration is accomplished via the Baseline Registration Module in the Data Management System. See Data Management System User Guide in this manual for specific directions.

3.E.2. Scheduling the Baseline Visit [Visit 3]

- The Baseline Visit must occur within 3 months of the Screening Visit. If it is not possible to schedule this within this period of time, Screening Visit procedures must be repeated. Contact the SDCC as to how to record this information and identify this participant in the Participant ID Log.
- Instruct participants to fast for 8 hours prior to the Baseline Visit. This is required for the blood draw. Fasting is NOT required for the I-GFR test. If a participant is selected for the subcohort I-GFR testing procedure, they are required to limit the meal that precedes the test to a low (< 10 grams) protein breakfast or lunch.
- Instruct participants to bring 24-hour urine specimen and completed DHQ. (See INSTRUCTIONS FOR BASELINE VISIT).

- Instruct participants to bring all of their recent [within the last 30 days] prescription and non-prescription medications with them to the Baseline Visit so that they can be identified for collection of concomitant medication information.
- Consider that scheduling the Iothalamate-GFR (GFR) test may require coordination with the GCRC or center wherein participants are being test for GFR. If participants are scheduled to have the GFR test and Baseline Visit on the same day, it may be desirable to arrange to have their CRIC Study blood specimens drawn during the initial phase of the GFR test so that the participant can have a low protein (< 10 grams) meal or snack, as permitted by the GFR protocol.
- Note: Scheduling tests for other procedures such as GFR, ECHO and EBT will require coordination with these departments. Consider this as well as the location of these testing centers in advance when scheduling participants.

Schedule of Major Tests

	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
	Baseline	6 Mos	12 Mo	18 Mos	24 Mos	30 Mos	36 Mos	42 Mos	48 Mos	54 Mos	60 Mos
ALL Participants	ECG		ECG ECHO		ECG		ECG		ECG ECHO		ECG
SUBCOHORT Participants	GFR		EBT		GFR				EBT GFR		
	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic

3.F. Baseline Visit [Visit 3]

3.F.1. Material Required for Baseline Visit [Visit 3]

Activities and Procedures:

Eligibility confirmation

Medical History

Blood draw [130 cc]

Collect 24 hour urine sample

Collect nail specimen

Physical measures: Blood pressure, Ankle Brachial Index, Anthropometry, BIA

ECG

Concomitant Medications

Questionnaire completion: Physical Activity, Symptom List, Kidney Disease Quality of Life, Beck Depression Inventory, Modified Mini Mental State Exam, Diet History Questionnaire

GFR [Subcohort only]

Equipment:

Supplies for drawing, processing, storing and shipping all specimens

Urine measurement and collection container

Nail clippers and container

Urine Pregnancy test (prior to GFR test if selected for the subcohort, for all women of childbearing age)

Sphygmomanometer, tape measure, blood pressure cuffs and doppler

BIA and electrodes

ECG and supplies

MMSE supplies

GFR supplies

The Baseline Visit must occur within 3 months of the screening visit and will consist of the tests and procedures described below. The RC should advise the participant to allow approximately 4 hours for the Baseline Visit. An additional 4 hours should be allotted if the participant was assigned to the GFR subcohort. The GFR testing may occur on the same day as the Baseline Visit or be scheduled for another day depending on the participant's availability, though it should occur as soon as possible.

- The RC will collect the 24 hour urine sample and the completed Diet History Questionnaire [DHQ]. If the 24 hour urine sample volume is less than 500 cc or if the total collection time is less than 23 hours, the test must be repeated.
- The participant will be instructed to fast for at least 8 hours prior to their Baseline Visit. Blood and urine will be collected according to Appendix B – Laboratory Procedures. The amounts and types of specimens collected will be recorded on the **Specimen Collection [SPECIMEN]** form. In the event the participant arrives having not fasted, the time and date of their last meal will be recorded and specimen collection will proceed.
- The participant will have a series of physical measurements including height, weight, and waist measurements, Ankle Brachial Index calculation, and Bioelectric Impedance Assessment. These measurements will be recorded on the **Physical Assessment [PHYASSESS]** form.
- The participant will have their blood pressure measured and recorded on the **BP** form following the procedure outlined in Appendix A of this manual. The RC will record the pulse and 3 sequential BP measurements while the participant is seated, followed by the pulse and one BP measurement while standing.

- The participant will have an ECG performed according to the procedure outlined in Appendix C of this manual. ECG will be read at the clinical center within 24 hours of acquisition by the investigator or their designee. If any of the Urgent Alert values are identified [See Appendix C], the RC must complete the Urgent Alert **[ALERT_U]** form and notify the primary care physician or health care provider as indicated on the form.
- The participant will be instructed to bring all prescription and non-prescription medication they have taken in the last 30 days with them to the baseline visit. The RC will record the medications, noting total daily dose, unit, frequency and route, on the **Concomitant Medication [CMED]** form.
- If the participant does not bring their medication with them, the RC will collect this information through participant interview. A follow-up phone call to the participant may be necessary to confirm the accuracy of the interview results.
- Complete the **Medical Event [EVENT]** form by inquiring if any of the listed medical events or procedures have occurred since the Pre-screening Visit.
- The participant will be asked to complete a series of questionnaires including the **Beck Depression Inventory [BDI],** the **Kidney Disease and Quality of Life [KDQOL]**, a **Physical Activity Assessment [PHYACT]**, a **Symptom List [SYM]**, and a comprehensive **Medical History [MEDHX]** form.
- The RC will administer the **Modified Mini-Mental State Exam [MMSE]** according to the instructions outlined in Appendix E.
- The forms listed above may be completed independently by the participant or the RC may assist the participant by reading the questions and recording their answers. It is expected that some forms, MEDHX in particular, may require RC assistance in interpreting clinical questions. The mode of questionnaire administration, either self administered or interviewer–administered, must be indicated on the form. The RC should indicate interviewer-administered if their assistance is required in completing any significant portion of a questionnaire.
- If participants have difficulty answering a particular question, they should be instructed to make their best estimate rather than leaving a response blank. The RC should review all participant completed questionnaires for completeness and legibility prior to the participant's departure.
- The RC will review all participant and healthcare provider contact information, making the appropriate updates, prior to concluding the Baseline Visit.

3.G. Telephone Contacts [6, 18, 30, 42, 54 Months]

Activities and Procedures:

Contact Information Update

Concomitant Medications

Medical Event Information

Participants will be contacted by telephone approximately 6 months after the baseline visit and each annual clinic visit. The purpose of the call is to update contact information, recent medical events and concomitant medication use. This is an opportunity to discuss the CRIC Study schedule with the participant and to remind him/her about the upcoming clinic visit. The RC may want to schedule the next clinic visit and tests at this time if the participant is willing to do so.

Note that some participants may be involved in ancillary studies that they may wish to discuss or they may have recently been contacted by CRIC Study personnel to answer questions related to a CRIC ancillary study. The RC should be informed whenever a CRIC Study participant who has been enrolled at their site is being contacted for information or participation in an approved ancillary study so that telephone contacts may be coordinated if at all possible.

3.H. Annual Visits

The RC should begin contacting participants 2 months prior to their annual visit. Visit windows are minus and plus 2 months of the target date, therefore, contacting participants early in the visit window allows the RC maximum flexibility in scheduling appointments or time to locate missing participants. The Data Management System provides Calendar Tools for Scheduling to assist in scheduling participants. The RC will arrange to forward the 24 hour urine specimen collection kit, instructions and when applicable, Diet History Questionnaire [DHQ] to the participant to be completed prior to the annual visit.

In the event the participant has relocated to an area from which it is no longer feasible to travel to the clinical center, the participant will be asked to permit study personnel to contact them annually by telephone. Every effort should be made to encourage continued participation. The RC should follow the format described for telephone contact.

3.H.1. Annual Clinic Visit – 12 Months

Activities and Procedures:

Medical Record Consent

Contact Information Update

Medical History Update

Medical Event Information

Blood draw [130 cc]

Collect 24 hour urine sample

Collect nail specimen

Physical measures: Blood pressure, Ankle Brachial Index, Anthropometry

Concomitant Medications

ECG

EBT [Schedule for Subcohort only]

Questionnaires: Symptom List, Kidney Disease Quality of Life

Echocardiogram [Schedule]

Equipment:

Supplies for drawing, processing, storing and shipping all specimens

Urine measurement and collection container

Nail clippers and container

Sphygmomanometer, tape measure, blood pressure cuffs and doppler

ECG and supplies

Echocardiogram supplies

- The RC will collect the 24 hour urine sample. If the 24 hour urine sample volume is less than 500 cc or if the total collection time is less than 23 hours, the test must be repeated.
- The participant will be instructed to fast for at least 8 hours before this baseline visit. Blood and urine will be collected according to procedures described in Appendix B of this manual. The amounts and types of specimens collected will be recorded on the **Specimen Collection [SPECIMEN]** form. In the event the participant has not fasted, the time and date of their last meal will be recorded and specimen collection will proceed.
- The participant will have a series of physical measurements including height, weight, and waist measurements, Ankle Brachial Index calculation. The measurements will be recorded on the **Physical Assessment [PHYASSESS]** form.
- The participant will have an ECG performed according to the procedure outlined in Appendix C. The ECG will be read at the clinical center within 24 hours of acquisition by the investigator or their designee. If any of the Urgent Alert values are identified, the RC must complete the Urgent Alert **[ALERT_U]** form and notify the primary care physician or health care provider as indicated on the form.
- The Participant will have their blood pressure **[BP]** measured following the protocol outlined in Appendix A. The RC will record the pulse and 3 sequential BP measurements while the participant is seated followed by the pulse and one BP measurement while standing.
- The participant will be instructed to bring all prescription and non-prescription medication they have taken in the last 30 days with them to annual clinic visits. The RC will record the medications, noting total daily dose, unit, frequency and route, on the **Concomitant Medication [CMED]** form.
- If the participant does not bring their medication with them, the RC will collect this information through participant interview. A follow-up phone call to the participant may be necessary to confirm the accuracy of the interview results.

- Complete the **Medical Event [EVENT]** form by inquiring if any of the listed medical events or procedures have occurred since the 6 month telephone contact. If the medical event or procedure occurred more than 6 months ago and it has not been documented on a previous EVENT form, include it at this time.
- The participant will be asked to complete the following questionnaires: **Kidney Disease and Quality of Life [KDQOL]**, a **Symptom List [SXLIST]**, and a follow-up **Medical History [MEDHXFU]** form.
- These forms may be completed independently by the participant or the RC may assist the participant by reading the questions and recording their answers. It is expected that some forms, MEDHXFU in particular, may require RC assistance in interpreting clinical questions. The mode of questionnaire administration, either self administered or interviewer–administered, must be indicated on the form. The RC should indicate interviewer-administered if their assistance is required in completing any portion of a questionnaire.
- If participants have difficulty answering a particular question, they should be instructed to make their best estimate rather than leave a response blank. The RC should review all participant completed questionnaires for completeness and legibility prior to the participant's departure.
- The RC will review all participant and Healthcare provider contact information, making the appropriate updates, prior to concluding the annual visit.
- ECHO and EBT tests should be scheduled to coincide with this visit. (All participants should be scheduled for an Echocardiogram; only subcohort participants are scheduled for EBT.) If this is not possible, these should be scheduled as close to the visit date as possible. The maximum window for scheduling these tests are minus and plus two months of the target date.

3.H.2. Annual Clinic Visit - 24 Months

Activities and Procedures:

Medical Record Consent

Contact Information Update

Medical History Update

Medical Event Information

Blood draw [130 cc]

Collect 24 hour urine sample

Collect nail specimen

Physical measures: Blood pressure, Ankle Brachial Index, Anthropometry, BIA

Concomitant Medications

ECG

GFR [Schedule for Subcohort only]

Questionnaire completion: Physical Activity, Symptom List, Kidney Disease Quality of Life, Beck Depression Inventory, Modified Mini Mental State Exam, Diet History Questionnaire

Equipment:

Supplies for drawing, processing, storing and shipping all specimen urine measurement and collection container

Nail clippers and container

Sphygmomanometer, tape measure, blood pressure cuffs and doppler

ECG and supplies

GFR supplies

MMSE supplies

3.H.3. Annual Clinic Visits – 36 and 60 Months

Activities and Procedures:

Medical Record Consent

Contact Information Update

Medical History Update

Medical Event Information

Blood draw [130 cc]

Collect 24 hour urine sample

Collect nail specimen

Physical measures: Blood pressure, Ankle Brachial Index, Anthropometry

Concomitant Medications

ECG

Questionnaires: Symptom List, Kidney Disease Quality of Life

Equipment:

Supplies for drawing, processing, storing and shipping all specimens

Urine measurement and collection container

Nail clippers and container

Sphygmomanometer, tape measure, blood pressure cuffs and doppler

ECG and supplies

3.H.4. Annual Clinic Visit - 48 Months

Activities and Procedures:

Medical Record Consent

Contact Information Update

Medical History Update

Medical Event Information

Blood draw [130 cc]

Collect 24 hour urine sample

Collect nail specimen

Physical measures: Blood pressure, Ankle Brachial Index, Anthropometry, BIA

Concomitant Medications

ECG

ECHO [Schedule]

EBT [Schedule for Subcohort only]

GFR [Schedule for Subcohort only]

Questionnaire completion: Physical Activity, Symptom List, Kidney Disease Quality of Life, Beck Depression Inventory, Modified Mini Mental State Exam, Diet History Questionnaire

Equipment:

Supplies for drawing, processing, storing and shipping all specimens

Urine measurement and collection container

Nail clippers and container

Sphygmomanometer, tape measure, blood pressure cuffs and doppler

ECG and supplies

ECHO and supplies

EBT supplies

GFR supplies

BIA and supplies

MMSE supplies

4. Visit Administrative Information

4.A. Screening Failures and Re-Screening Requirements

Participants who fail to meet the eligibility criteria following either the Pre-screening or Screening Visit may be re-screened at the discretion of the investigator, depending on the particular exclusion criterion. **Sites should wait a minimum of 6 months before re-screening participants** in an effort to conserve resources. As stated previously, a new participant ID should be assigned when re-screening participants.

4.B. Participant Calendar

Prior to completing the baseline visit, the RC will provide the participant with a calendar indicating the projected telephone contacts and clinic visit dates. Each date will indicate a visit window of 2 months before and 2 months after the projected visit date. The RC should make every effort to complete the contact with the participant within this window. In the event that the RC is unable to schedule a clinic visit or make contact with the participant within the 4 month window, every effort should be made to complete the contact as soon as possible prior to the next scheduled contact.

4.B.1. Missed Visits

A visit is considered "missed" when the RC has tried unsuccessfully to complete a telephone contact or clinic visit within the visit window, which is 4 months. **For example:**

CRIC STUDY VISIT		DATE	RANGE	INFORMATION
Visit 1	Prescreening Visit	May 1, 2003	---	There are no time limits on the period between Prescreening and the Screening Visit
Visit 2	Screening Visit	May 20, 2003	---	Baseline visit must be completed within 3 months of the Screening Visit date.
Visit 3	Baseline Visit	June 15, 2003 **	Up to August 20, 2003	**Calendar tool will calculate all subsequent dates and windows starting with June 15, 2003
Visit 4	6 Month Telephone Follow-up	December 15, 2003	October 15, 2003 to February 15, 2004	Visits conducted within this time frame will be considered 'on time.' Those conducted outside of the time frame will be considered 'out of range.'
Visit 5	12 Month Clinic Follow-up	June 15, 2003	April 15, 2004 to August 15, 2004	

All participant contacts should be considered opportunities to collect CRIC Study information. As a result information acquired during a phone follow-up that is outside of the visit window should still be collected and entered into the database. Information should be associated with the preceding visit up to and until the next visit window [telephone contact or clinic visit] begins.

4.C. Participant Withdrawal

The RC will complete a **Withdrawal [WITHDR]** form when a participant completes their final study visit at the end of 6 years **or** at any time prior to the year 6 visit if the participant wishes to withdraw from the study. Reasons for premature termination include participant death, participants who are lost to follow-up and participants who are too ill or no longer wish to participate. Participant's have the right to request that their stored specimens be destroyed. The RC should ask the participant about each type of stored specimen (serum, DNA samples, urine and nail specimens) and indicate this information on the [WITHDR] form. A copy of this form will be sent to the CRIC Central Lab requesting specimen disposal. The lab will return the completed form indicating when the specimens were disposed of for the participant's record.

4.D. Participant Transfers

It is possible for a CRIC Study participant to transfer to another participating Clinical Center or site during the course of the study. However, it is preferred from a scientific as well as operational point of view, that a participant complete the study at the same Clinical Center and site in which (s)he was enrolled. Participants ***cannot*** transfer to another Clinical Center during the Pre-Screening and Enrollment Phase (Prescreening, Screening and Baseline Visits) of the study.

To transfer a participant:

The RC at the Originating Center will contact the RC at the Receiving Center to inform him/her of the transfer and the participant's next scheduled visit date. The RC at the Receiving Center will provide the participant with contact information for the Receiving Center, complete **Participant Transfer [TRANS]** form, and send copies of the participant's study folders, medical records and TRANS to the Receiving Center.

Because of the disclosure of personal identifying information required to transfer a participant to another clinical center, it may be necessary to complete the informed consent process and form, and the HIPAA authorization form before making transfer arrangements.

The RC at the Receiving Center will contact the participant to confirm the next scheduled contact and provide the RC and PI contact information.

- Review Clinical Center-specific Informed Consent with the participant.
- Have the participant sign Clinical Center-specific Informed Consent.
- Complete the remainder of ***TRANS***.
- Send a copy of ***TRANS*** to the Scientific Data Coordinating Center (***SDCC***).
- Complete ***PTCONT***.

The unique Participant ID, assigned to the participant at the Originating Center, remains unchanged during transfer and will be used at the Receiving Center to identify the participant. The Receiving Clinical Center will use their assigned Clinical Center and Site codes on all study-related CRFs and communications once the transfer is complete.

In case of a temporary transfer (limited to a random visit) where the participant needs to be seen at a participating Clinical Center or Site on a temporary basis, the Originating Center RC will contact the Receiving Center RC and share relevant information (e.g. visit number, medical issues, etc.) with the RC. (S)he will also notify the SDCC and the SDCC will review the procedures with both RCs to facilitate a smooth transition.

Relevant correspondence and completed administrative CRFs for the transfer process will be filed in the participant binder/folder.

5. Data and Administrative Forms

5.A. Case Report Forms

5.A.1. Acquisition of Case Report Forms from the SDCC

Data and Administrative Case Report Forms **(*CRFs*)** are provided to the sites in electronic format on the CRIC website and Data Management System **(DMS)** as PDF (portable document format) files. Each site is responsible for printing all data and administrative CRFs. CRFs can be printed on NCR paper. CRFs necessary for each visit are grouped together, to streamline the printing process. Data CRFs and Administrative CRFs are also available individually.

5.A.2. General Instructions for the Completion of Case Report Forms

5.A.2.(a). General Instructions for all Case Report Forms

1. Two types of CRFs are used for this study:
   - **Data CRFs** - contain participant data and are entered in the database.
   - **Administrative CRFs** – are used for study organization and not entered in the database.

   A CRF is a data entry CRF unless it is identified as Administrative directly under the CRF heading. The RC should check the CRFs in a packet against the Recruitment Chart or Follow-up Chart to confirm that all CRFs are available before a clinic visit or telephone contact with the participant. Missing CRFs in a visit packet should be printed from the website or the DMS prior to the visit. As form changes occur, sites will be notified and current versions of forms will be made available on the website and the DMS.
2. General instructions:
   - All CRFs should be completed in ***black*** ink. Do not use pencil, blue ink.
   - Responses should not be left blank. **UNK** should be filled in any space left unanswered.
   - If the participant is unsure of a response, he/she should use his/her "**best estimate**" rather than leave the question unanswered.
   - It is important that the RC complete the header information ***before*** administering the CRFs to insure easy identification in case of separated pages, or multiple participant visits in a day.

- Participant ID number will be determined on the Participant ID Log [PTIDLOG] during screening.
- The RC is responsible for reviewing all completed CRFs.
- All personal identifiers should be obscured or "blacked out" from copies of laboratory results, procedure reports and other source documents and study identifying information. Participant ID and Participant Initials should be recorded prior to forwarding copies to the SDCC, if requested. ***All originals should retain personal identifying information.***

3. Participant Completed Case Report Forms
   - "Participant completed" CRFs are self-reports, to be completed by the participant.
   - The RC should be available to answer any questions that the participant may have.
   - The RC may interview participants who require assistance in completing the CRFs.
   - For each participant completed CRF, the RC should check the appropriate box to indicate whether CRF was self-administered or interviewer-administered.
   - Since the participant may find some of the information on the CRFs to be sensitive, whenever possible, the participant should be encouraged to complete the CRFs unassisted.
   - Before the participant leaves the clinic, the RC should review the CRFs for legibility and completeness.
   - After the RC reviews the CRFs, the RC should complete the RC ID number in the header.
4. Research Coordinator Completed Case Report Forms
   - These CRFs are ***not*** completed by the participant, but are administered to the participant by the RC, by interviewing the participant and asking specific questions on the CRFs.
   - The RC is responsible for getting an appropriate response from the participant if the participant's response is unclear, incomplete, or irrelevant.
   - The RC should use "probing" technique to refocus and redirect the participant's attention to the question.
   - The interviewer should get the participant to elaborate or reconsider an incomplete or inappropriate response, without leading the participant or influencing the content of the response (creating bias in his/her response).
   - Some questions addressed in the CRFs are personal and may be sensitive issues for the participant. When a participant shows reluctance in

answering a question, the interviewer should reassure the participant about maintaining confidentiality of the response and the importance of the question.

- All CRFs to be completed by the RC or the PI should be completed during the visit, unless awaiting a report (e.g. laboratory results).
- The RC should review the CRFs for completeness and legibility before the participant leaves, in case additional information or clarification is needed.

5. Review of Completed CRFs
   - The RC should review all CRFs for legibility, accuracy, and completeness ***before*** they are entered into the database.
   - If the RC identifies an error while reviewing the CRFs, the error should be corrected on the completed CRF by crossing out the error with a single line in ***black*** ink, entering the correct information, initialing and dating the change.
   - The RC should circle the correction for clarification, if necessary.

5.A.2.(b). Time frame for completion and data entry of CRFs:

The time frame for completion and data entry of CRFs is ***two (2) weeks*** from the date of collection. ALERT_I and ALERT_U must be completed and data entered as soon as possible.

5.A.2.(c). General Coding Issues:

- Date: Date will be entered in the MM/DD/YYYY format. Year will be recorded as 4 digits (e.g. 1997, 2001).
- Time: Time will be recorded in the 24-hour clock format (e.g. 1:00 in the afternoon is 13:00 hours).
- Data fields: Units of measurements or reporting have been added to each data field, where necessary, to capture accurate values for the data field (e.g. ___ ___ ___ / ___ __ ___ mmHg for blood pressure; __ __ years old).

Header Information:

Participant ID: This is determined by the RC and logged in the Participant ID Log [**PTIDLOG**] at each Clinical Center and site.

Participant ID is an eight-digit number, with a separator after the second and the fourth digit:

The first two (2) digits are unique IDs assigned to each of the Clinical Centers, identified in the protocol.

The Clinical Centers identified in the protocol are:

01 University of Pennsylvania Medical Center, Philadelphia, PA
02 The John Hopkins University, Baltimore, MD
03 Case Western Reserve University, Cleveland, OH
04 University of Michigan at Ann Arbor, Ann Arbor, MI
05 University of Illinois at Chicago, Chicago, IL
06 Tulane University Health Science Center, New Orleans, LA
07 Kaiser Permanente of Northern California, San Francisco, CA

The next two (2) digits represent the site(s) associated with each Clinical Center, including the "Primary" Clinical Center.

The ***Site*** numbers (with their corresponding "Primary" Clinical Center numbers, in parenthesis) identified to-date are:

(01) **01** University of Pennsylvania Medical Center
(02) **01** The Johns Hopkins Medical Institutions
(02) **02** University of Maryland
(03) **01** Case Western Reserve University
(03) **02** University Hospitals of Cleveland
(03) **03** Metro Health Medical Center
(03) **04** Cleveland Clinic Foundation
(04) **01** University of Michigan at Ann Arbor
(04) **02** St. John's Health System
(04) **03** Wayne State University / Detroit Medical Center
(05) **01** University of Illinois at Chicago
(06) **01** Tulane University Health Science Center
(07) **01** Kaiser Permanente of Northern California
(07) **02** University of California, San Francisco

The last four (4) digits are participant ID starting with 0001, assigned sequentially to each potential participant (e.g. 0002, 0003) who verbally agrees to CRIC Study processes at Prescreening Contact (***Visit #1***).

Once assigned, a participant ID is ***not*** deleted or transferred to another study participant.

Participant Initials: First letter from each of the participant's first, middle and last name are noted in the space provided for the initials. An "***X"*** is used when the participant does not have a middle name (e.g. Participant John Smith = J***X***S).

Visit Number: Screening and follow-up contacts have been identified in the protocol when specific events occur during the course of the CRIC Study. These contacts have been translated into Visit Numbers.

CRF Date: This is the date of the clinic visit or telephone contact when the CRIC Study procedure is completed.

RC ID: RC ID is a combination of 4-digit numbers to identify a Research Coordinator from a specific site, who will complete visit-specific assessments.

5.A.2.(d). Specific Instructions for Data Case Report Forms

This section provides specific instructions on how to complete each data CRF. If, after consulting this section, you are still unsure about CRF completion, please contact the CRIC Study Data Manager(s) at the SDCC.

Pre-Screening Data Case Report Forms

Prescreening Information [PRESCR]

Purpose: Prescreening of a potential participant to determine general study eligibility, based on broad inclusion/exclusion CRIC Study criteria.

Who: Research Coordinator.

When: Completed at Prescreening Contact (*Visit #1*) only; involves direct contact with the participant, either by phone or in-person.

Directions: Prior to contact, each potential participant will be assigned a study ID, which is the next sequential number on the Participant ID Log [*PTIDLOG*]. If the participant meets the study criteria, this Participant ID will be used to identify this participant for all future assessments in the study.

Q.1: A site-specific script (SCRIPT1), briefly explaining the CRIC Study, has been developed.

If the participant is contacted by telephone, verbal consent ***must*** be obtained, signed and dated by the interviewer, in the space provided on ***SCRIPT1***.

Verbal consent must also be obtained from the potential participant during in-person contact.

A potential participant must be made aware that the data collected at this time will be reported, and also reassured that s(he) will not be identified in the reports.

Q.2-5: These questions confirm basic demographic information that may have been collected on the Health Data Review **[HDREV]** CRF.

Q.6: Diagnosis of diabetes mellitus given by a healthcare provider.

Q.7: Noting the participant's response to this question, the RC determines if the participant is institutionalized.

Q.8a-g: Refer to the inclusion/exclusion criteria script Exclusion Script **[SCRIPT2]** developed for the RCs to discuss exclusion criteria with potential participants.

Q.9a: Refer to the list below of immunosuppressive drugs in renal disease.

IMMUNOSUPPRESSIVE DRUGS IN RENAL DISEASE

Therapeutic Name	Generic Name	Brand Name
Antineoplastic Agent	Cyclophosphamide	Cytoxan
Immunosuppressive Agent	Cyclosporine/CYA/Cyclosporin A	Gengraf
Immunosuppressive Agent	Cyclosporine/CYA/Cyclosporin A	Neoral
Immunosuppressive Agent	Cyclosporine/CYA/Cyclosporin A	Sandimmune
Immunosuppressive Agent	Azathioprine	Immuran
Immunosuppressive Agent	Tacrolimus/FK506	Prograf
Immunosuppressive Agent	Mycophenolate Mofetil	Cellcept
Antineoplastic Agent	Chlorambucil	Leukeran
Adrenocorticosteroid	Prednisone	

Q.9a-d: Refer to the inclusion/exclusion criteria script Exclusion Script **[SCRIPT2]** developed to discuss exclusion criteria with potential participants.

Q.10: This question will allow the RC to probe for other serious medical conditions that may prevent or may exclude the participant from considering CRIC Study. Space is provided to record this information to discuss, if necessary, with the PI.

Q.11: This question allows the RC to determine if the participant is enrolled in another trial. Depending on the type of trial he/she is enrolled in, the RC can determine if it will interfere with participation in the CRIC Study.

Space is provided to record this information to discuss, if necessary, with the PI.

Q.12: The RC should discuss participant responses that are questionable with the study PI to determine eligibility.

If the participant apparently qualifies (***Not ineligible***), he/she should be scheduled for Screening Visit (***Visit #2***).

If the participant does not qualify (***Ineligible***), the RC should end the screening contact.

Q.12a: If the participant qualifies but ***refuses*** participation, the RC should complete Prescreening Refusal [***PREREF***] CRF.

Additional space to record general comments has been provided at the bottom of page 2.

The RC should review participant's responses for completion and legibility prior to terminating the Prescreening Contact.

Although the participant may refuse to answer certain questions at this contact, leaving certain data unavailable for entry, available data collected on ***PRESCR*** will be entered in the prescreening module in the Data Management System (***DMS***). See the Data Management System User Guide in this manual for more information.

NOTE: All Participants must have a Prescreening form. The entire form must be completed in writing. The following procedures minimize the data entry process:

1. Form is single entry ONLY.
2. Form must be entered into the Data Management System [DMS] on or before the Screening Visit.
3. If a participant refuses the prescreening contact, enter Q1 in the DMS.
4. If a participant agrees to the prescreening contact, enter Q1 - 6 and Q12 in the DMS. [If a participant is eligible, enter no additional data.]
5. If a participant is ineligible, enter the question between 7 and 11 that excluded them.

Prescreening Refusal [PREREF]

Purpose: Terminate a potential participant who meets the study criteria, but refuses study participation.

Who: Research Coordinator.

When: Completed at Prescreening Visit (*Visit #1*) only; reasons for refusal are specific to Prescreening Contact.

Directions: The outcome of the Prescreening Contact should help the RC and the PI determine if the participant is "Not Ineligible", indicating that based on the data available, the participant has met the broader criteria of the CRIC Study.

If the participant refuses to consider the next phase in recruitment, i.e. eligibility confirmation, the RC should terminate the participant at the Prescreening Contact.

Multiple reasons can be checked for the participant's refusal to consider the study.

Brief comments should be noted in the space provided for other reasons.

Participant ID assigned to a participant who refuses ***cannot*** be re-used.

Reason(s) for refusal checked on ***PREREF*** will be entered in the prescreening database module available in the Data Management System (***DMS***).

Study Data Case Report Forms

Immediate Alert [ALERT_I]

Purpose: Report potential serious medical problems or emergencies, based on clinical observation or reported study information, and appropriate disposition.

The site RC and/or PI must report results and outcomes to the participant's primary care physician.

Who: Research Coordinator/Principal Investigator.

When: "As needed" CRF; upon identification of immediate alert information associated with CRIC Study clinical visits and tests.

Directions: Specific alerts have been identified in the protocol and may be encountered at the time of a clinic visit. When reporting such events, the RC may need to check "Yes" for only a few alerts/items listed on the CRF. Remaining alerts not encountered at the time of the exam by the RC must be checked as "No". Items cannot be left unanswered.

Q1: Date of Alert should indicate date of CRIC Study Visit.

Q.2a-b: Records observed elevated Systolic (>180) and Diastolic (>110) blood pressure during examination at a visit. If both are elevated Q.2a and Q.2b should be checked as "Yes". If one of the 2 measures is elevated, the elevated reading should be checked "Yes" and the normal reading should be checked as "No".

Q.3a-b: Acute distress is restricted to 3 items:

Chest pain

Severe respiratory distress

Acute neurological symptoms

Other symptoms determined as acute by the PI or the RC are noted under "Other" category and specified in the space provided.

Items must be checked as "Yes" or "No", and cannot be left unanswered.

Q.4a-b: The date of the ECHO and the reading (Central or Local) will be coded in items 4bi-4bvi.

Q.5a-d: Responses recorded here indicate the appropriate disposition of the medical alert. The PI/RC will indicate if the medical information was transmitted to the participant's primary MD through oral and written communication.

Q.6: The participant may or may not be made aware of the medical emergency, before the confirmatory results are available. It is the responsibility of the RC/PI to inform the participant of the outcome, e.g. Echocardiogram results, etc.

N/A response to this question may be checked if the participant was aware of the problems and the outcome did not involve reporting test results.

Completion of ***ALERT_I*** CRF may require an event investigation/confirmation, and completion of ***EVENT*** CRF.

ALERT_I data should be entered and verified in the Data Management System (***DMS***) as soon as possible.

This CRF is available for data entry in the DMS as a "Single CRF", indicating "as-needed" data entry.

Urgent Alert [ALERT_U]

Purpose: Report significant abnormal laboratory result or clinical process outcome from the Central Laboratory or Central (ECG) Reading Center.

The site RC and PI must report results and outcomes to the participant's primary physician.

Who: Research Coordinator / Principal Investigator.

When: "As needed" CRF.

Directions: Laboratory tests and Electrocardiogram performed at a clinic visit are sent to the Central Laboratory and Central ECG Reading Center (CERC). Specific alerts have been identified in the protocol for laboratory results performed at Central Laboratory and for the electrocardiogram read locally. Alert values will be made available to the sites as soon as possible through the Lab Status module in the DMS.

The RCs should transcribe information from lab results and local ECG interpretation onto the Urgent Alert (ALERT_U) CRF and also note actions taken to inform the participant and his/her primary care physician, through oral or written communication.

When reporting such results, it may be necessary to check "Yes" for one, two or several alerts/items listed on the CRF. Remaining alerts not reported at the visit by the RC must be checked as "No". Items cannot be left unanswered.

Q.1: Date of Alert will be the date the abnormal value is reported by the Central Laboratory or Central Reading Center. Note: The CRF date in the header will be the date that the RC completes ALERT_U.

Q.2: Laboratory results, other than those listed on the CRF, determined as abnormal will be noted as "Other" and identified in the space provided.

Q.3: Abnormal readings from a local interpretation of the ECG will be noted on ALERT_U.

Q4a-b: Responses recorded here indicate the appropriate disposition of the medical alert. The PI/RC decide how to transmit information about the medical emergency with the participant's primary MD through oral and written communication.

Q.5: The participant may or may not be aware of the abnormal results at the time of the visit. It is the responsibility of the RC/PI to inform the participant.

N/A response to this question may be checked if the participant was aware of the problems and the outcome did not involve reporting test results.

Completion of ***ALERT_U*** CRF may require an event investigation/confirmation, and completion of ***EVENT*** CRF.

ALERT_U data will be entered and verified in the Data Management System (***DMS***) as soon as possible.

This CRF is available for data entry in the DMS as a "Single CRF", indicating "as-needed" data entry.

Participant Assignment [ASSIGN]

Purpose: Assign a consented and eligible participant to the CRIC Study and sub-cohort, based on age, race, gender, and e-GFR value.

Who: Research Coordinator.

When: Completed after Screening Visit *(Visit #2)*.

Directions: The following 3 CRFs collected during the Screening Visit [Visit #2], Eligibility Assessment [*ELIG*], Screening Laboratory Results [*SCRLAB*] and Demographic Information [*DEMO*], *must* be entered *and* verified in the DMS prior to completing Participant Assignment CRF [ASSIGN].

Step I – eGFR Module:

eGFR value will be calculated electronically within the eGFR module in the Data Management System (DMS) on the ASSIGN screen, based on data available from entering and verifying ELIG, SCRLAB and DEMO.

The *ASSIGN* screen will provide step-by-step instructions for the Research Coordinator to follow.

By clicking on the eGFR button on the ASSIGN screen, eGFR value will be displayed on the screen. This value will be recorded on the ASSIGN CRF.

Participant ID will be entered into the eGFR module available on the screen. This will generate eGFR value that will be recorded on ***ASSIGN*** CRF.

Step II – Participant Assignment:

Participant Assignment will be determined by clicking on the Participant Assignment module on the screen. If the participant meets the Cohort and sub-cohort criteria, the data available on the screen for item #s 2, 3 and 4 will be recorded on ***ASSIGN*** CRF.

The screen will then prompt the RC to verify assignment outcome data in item #s 2, 3 and 4 by clicking on the Verification module.

Step III – Outcome:

When the verification process is complete, the RC will contact the participant to inform him/her about the study assignment and schedule Baseline Visit [***Visit #3***].

If the participant is interested in continuing with the study, the assignment outcome will be discussed with the participant and study procedures will be reviewed and the next visit scheduled.

If, at this time, the participant decides to discontinue participation in the study, the RC will complete the Withdrawal [***WITHDR***] CRF, checking the primary reason for termination from the study.

If the participant does NOT qualify for the cohort based on the age/eGFR criteria (Q #2 is No / 0), the RC will complete the ASSIGN CRF based on the data displayed on the screen and verify this data by clicking on the VERIFICATION button.

Beck Depression Inventory [BDI]

Purpose: Determine depressive symptoms of participants in the CRIC Study.

Who: Participant, as a self-report.

When: Completed at Baseline Visit *(Visit #3)*,
24-month follow-up (Visit #7) and
48-month follow-up (Visit #11).

Directions: Beck Depression Inventory is a self-report form. The participant completes a twenty-one question survey, rating statements (feelings) on the scale of 0 to 3.

A participant can circle more than one response per statement. If multiple responses are checked per statement, the highest value circled per question is entered in the DMS. The participant must be instructed to rate his/her feelings in the past 7 days. Total score will be generated electronically by the DMS and will not be noted on the questionnaire.

Q.9: Particular attention will be paid to the response of "3" on Question #9. ***A response of "3" suggests that the participant may have suicidal thoughts***. The PI (or a PI designee, a Psychologist or Psychiatrist) should be consulted to verify that the participant will ***not be a danger to him or herself*** after leaving the site.

The RC will check responses for completion and legibility.

If the questionnaire is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

BDI data will be entered and verified in the Data Management System (***DMS***).

Concomitant Medications [CMED]

Purpose: Record all prescription and non-prescription medications/supplements/vitamins currently taken by the participant in the 30 days preceding a contact or a visit.

Who: Research Coordinator.

When: Completed at each clinic visit and telephone contact.

Directions: Each contact or visit will generate a list that will remain independent of other contacts or visit. CMED information provided at previous visits will not be reviewed at the current visit.

Medications refer to prescription or non-prescription drugs, over-the-counter drugs, vitamins, nutritional supplements or herbal remedies.

Starting at Baseline Visit (***Visit #3***) and continuing until Month 60 follow-up (Visit 13), any medications (new or on-going) taken in the 30 days preceding clinic visit or telephone contact should be recorded. This can be achieved by requesting the participant to either maintain a list of medications or bring the medications to the clinic visit.

RC should document drug name, drug code, total daily dose, unit, frequency and route of administration for each medication that the

participant has taken. Multiple pages may be used to record medications.

Line Number: A sequential numbering, starting with 001 to record medications at a contact or visit. This numbering is used administratively in the DMS to identify a record and has no relevance to the CMED data.

Drug Code #: Drug code is obtained from the *Medication Reference* tool/module available in the Data Management System (*DMS*).

If a drug code for a concomitant medication that the participant has recorded is unavailable in the Medication Reference Tool in the DMS, the RC should call the Clinical Data Manager at the SDCC. If the Clinical Data Manager is unable to locate the information for the RC, the medication and other relevant data will be recorded on a log maintained at the SDCC and the Clinical Data Manager will develop a code and enter the data in CMED at the SDCC.

Medication Name: Medication Name is the generic name for participant's medication/treatment, generated from the *Medication Reference* tool.

Total Daily Dose (TDD): The RC must multiply the strength of the dose (the individual dose amount) by the total number of doses per 24 hours. When recording combination drugs the TDD column should record TDD for the "critical" component of the medication, e.g. Codeine for Tylenol 3.

Unit: Select the *most specific* response possible from the available legend.

Frequency: Select the *most specific* response possible from the available legend.

Route: Select the *most specific* response possible from the available legend.

Additional medications are recorded on ***CMED - Additional Page,*** available in the CRF module of the Data Management System ***(DMS).***

CMED data will be entered and verified in the Data Management System (*DMS*).

Demographic Information [DEMO]

Purpose: Collect participant demographic information and brief family history.

Who: Participant, as a self-report.

When: Completed at Screening Visit (*Visit #2*).

Directions: This questionnaire collects participant demographic information. Ethnic and racial background questions have additional questions that explore the family origin.

Q.2: Response from Q #2 in *DEMO* calculates eGFR in the ASSIGN module.

If a participant has selected the option "Other" for gender, upon review of the form the RC must make a determination of "Male" or "Female" based on birth gender and change the participant's response, using appropriate data correction technique. The change must also be documented on the Comments Sheet (*COMM*). This specification is required for eGFR calculation.

Q.7: Study participant has the option of checking "Yes" for more than one racial category. If a participant checks "Black/African American" and any other category, they will be identified for the purpose of eGFR calculation, as Black/African-American.

Q.8-10: Participant checking "Other" should specify the country of origin.

Q.12: The RC should be available to help a participant select the most appropriate category, if the participant is unsure where his/her occupation may fit in the categories provided. The categories provided are:

- ***Professional, executive occupation, business owners*** include CEOs, artists, athletes, entertainers, engineers, lawyers, accountants scientists
- ***Manager, technical occupations*** include social/religious workers, teachers, insurance/real estate/retail sales managers
- ***Clerical, sales, administrative support occupations, technicians*** include bank tellers, clerks, computer operators, dispatchers, office supervisors, receptionists, secretaries, teachers' aide
- ***Skilled labor*** include certified electrician, carpenter, welder, butchers, bakers, equipment repairers, mechanics, metal workers, plant/systems operators
- ***Semi-skilled labor*** include construction help, mechanic's help. crane operators, drivers, parking lot attendants, sailors/deckhands
- ***Unskilled labor*** include porters, bell hops, manual labor, farm labor,

- Home maker

Q.14: A diagnosis of diabetes mellitus should have been given by a health care professional.

The RC will check responses for completion and legibility.

DEMO data will be entered and verified in the Data Management System (***DMS***) as soon as possible.

This data is required to determine Participant Assignment for the CRIC Study and sub-Cohort.

Diet History Questionnaire [DHQ]

Purpose: Assess dietary factors associated with cardio-vascular disease progression in renal insufficiency.

Who: Participant, as a self-report.

When: Completed at Baseline Visit (Visit #3),
24 month-follow-up (Visit #7) and
48 month-follow-up (Visit #11).

Directions: The DHQ consists of a food list of 144 items, and collects information about use of dietary supplements. It includes frequency and portion size questions for each food in the list.

General instructions, listed on the cover page of the DHQ, will be reviewed with the participant. The DHQ takes about an hour to complete. The DHQ should be completed using a black ink pen

An audio aid and hotline are available through the CRIC Study to facilitate ease and accuracy in completing the questionnaire. The audio aid will guide the participant through each section of the DHQ with detailed instructions about estimating portion size and frequency of consumption. It will also provide assistance with skip patterns to reduce the number of missed questions.

All DHQs for a participant must be completed in the same manner (interviewer or self-administered) so within-person dietary changes can be examined without possible bias from method of administration.

CRIC Study participant identifiers will be written by the RCs prior to distributing or mailing the CRF to the participant.

DHQ should be given to the participant at Screening Visit (Visit #2), to be completed and returned at the Baseline Visit (Visit #3). A DHQ,

along with the cover letter and instructions, will be mailed (with pre-paid postage for return envelopes) to the participant ten days before the Baseline Visit, 24 month follow-up and 48-month follow-up.

When the completed CRF is returned to the RC, it will be checked for completeness and legibility of responses (blackened circles, blank responses) The RC will contact the participant to resolve questions or review illegible responses. The participant may be sensitive about his/her dietary habits. It is important for the RC to resolve inconsistencies in responses in a non-judgmental manner.

Clinical Center #07 (San Francisco area sites) will give an additional page to Asian American participants to assess intake of foods commonly found in Asian American diets that are not included in the DHQ.

Completed CRFs will be sent **monthly** to the SDCC for scanned data entry. FedEx forms to:

Marie Durborow
University of Pennsylvania
Clinical Research Computing Unit/CCEB
3535 Market Street, Suite 560
Philadelphia, PA 19104-3309

Eligibility Assessment [ELIG]

Purpose: Confirm potential participant's eligibility for participation in the CRIC Study and sub-Cohort(s).

Who: Research Coordinator or PI, as an interview.

When: Completed at Screening Visit (Visit #2) and reviewed at Baseline Visit (Visit #3).

Directions: This CRF confirms the inclusion and exclusion criteria established in the protocol. Shaded responses checked on the CRF will exclude the participant from the CRIC Study and sub-Cohort.

RCs should discuss medical history if the participant is unsure of the response. Most of the conditions listed in the exclusion criteria are based on the participant's self-report of past medical history.

Time limited criteria that may exclude a participant at the present may be re-evaluated for inclusion later, making the participant eligible for participation in the future.

The following are instructions to complete Cohort-related exclusion questions.

Q.1: Study processes cannot be administered to participants without a signed informed consent.

Q.4: Noting the participant's response to this question, the RC determines if the participant is institutionalized.

Q.5: Response to cirrhosis of the liver question is based on participant self-report.

Q.6: Response to polycystic kidney question is based on participant self-report.

Q.7: Response to this cancer of the kidney question is based on participant self-report.

Q.8: Response to multiple myeloma question is based on participant self-report.

Q.9: Response to HIV infection/AIDS question is based on participant self-report.

Q.10: Response to immunosuppressive drug use question is based on participant self-report. Use of immunosuppressive drugs in the past 6 months excludes a participant from the CRIC Study for this period of time only.

Q.11: Response to dialysis question is based on participant self-report. Dialysis in the past month excludes a participant from the CRIC Study.

Q.12: Response to kidney transplant question is based on participant self-report.

Q.13: Response to other organ or bone marrow transplant question is based on participant self-report.

Q.14: Response to treatment with chemotherapy question is based on participant self-report. Chemotherapy in the past 2 years excludes a participant from the CRIC Study for this period of time only.

Q.15: This question allows the RC to determine if the participant is enrolled in the AASK or KEEP Study.

NOTE: If a participant indicates that they are currently enrolled in a drug, device or diet study, the RC should gather information about this from the participant and discuss the matter with the investigator. If it appears that dual participation could have a detrimental effect on the participant, the investigator should contact the Adjudication Committee for review of the matter.

Q.16: This question allows the RC to determine if the participant is enrolled in another trial. Trials of therapeutic agents may have an effect on renal or cardiovascular outcomes (as assessed by the Adjudication Committee).

Q.17a-b: The RC should probe to determine if the participant experiences symptoms that would diagnose NYHA Class III or IV heart failure at baseline:

Class III Heart Failure (Moderate)

Patient Symptoms: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.

Class IV Heart Failure (Severe)

Patient Symptoms: Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

IMPORTANT NOTE: From their reported symptoms and other health problems, it may not be clear that a participant has a clinical classification of Class III or IV heart failure. Consult with the investigator/site physician as to the appropriate classification for participants who report heart failure.

Q.18a-b: A potential participant may consent to participate in the Cohort but may refuse to allow a specimen to be stored for genetic testing or refuse to provide their Social Security Number. If a participant indicates on the consent form that they do not agree to provide a blood specimen for any one of the genetic options available, check "NO" Question 18a. Permission for genetic testing and provision of SSN are **optional** processes for the Cohort.

The following are instructions to complete GFR sub-Cohort-related exclusion questions. Participants who do not qualify for the sub-Cohort are ***not*** excluded from participating in the CRIC Study.

Q.20: This criterion is confirmed for female participants only. N/A response is acceptable only for male participants or female participants who are post-menopausal. Source documentation must be available to confirm female participant's post-menopausal status.

Q.21: This criterion is confirmed for female participants only. N/A response is acceptable only for male participants or female participants who are post-menopausal. Source documentation must be available to confirm female participant's post-menopausal status.

Q22: This criterion is intended to defer participants who may have experienced recent radionuclide exposure. The most common example of this test is a thallium stress test.

Q.23-25: If a participant's response to Q.23 is "Yes", the participant does not qualify for subcohort participation. If 3 of the 5 criteria listed for Q.24 have a "Yes" response checked, the RC should consult the PI to determine if the participant meets urinary impairment criteria.

Q.26. Response to this question confirms that the participant qualifies to participate in the sub-Cohort.

Q.27: This question allows the RC and the PI to evaluate and judge the qualifying participant on his/her ability to follow through with the research processes. Based on past interactions and experiences with the participant, or their "clinical" judgment of the participant's situation, the RC and the PI may exclude the participant from the CRIC Study.

ELIG data will be entered and verified in the Data Management System (***DMS***) as soon as possible.

Encryption Information [ENCRYP]

Purpose: Maintain participant confidentiality by encrypting participant's Social Security Number in the Data Management System.

Who: Research Coordinator.

When: Completed at Baseline Visit (Visit #3).

Directions: The participant must sign consent for use of Social Security Number for research purposes. If the participant refuses consent, encryption process will not apply to the participant.

ENCRYPT data will be entered and verified in the Data Management System (***DMS***). The encryption module in the DMS provides a mechanism for encrypting Social Security Numbers.

- Enter participant's Social Security Number in the field labeled 'Social Security Number'.
- Press the button labeled 'Encrypt'.
- When the 'Encrypt' button is pressed, the encrypted number appears in the field labeled 'Encrypted Number'.
- When the encrypted number appears, record the encrypted number onto the Case Report Form.
- After the encrypted number has been transcribed to the Case Report Form, press the button on the screen labeled 'Re-Enter'.
- Pressing 'Re-Enter' will clear the field of the system-generated encrypted number.
- Enter the encrypted number from the Case Report Form into the now blank field on the screen labeled 'Verified Encrypted Number'.
- Press 'Verify' button on the screen. This will verify that entered encrypted number matches the encrypted number generated by the system.
- If the numbers match, the user will be given a message indicating that the number entered is correct. However, if the numbers do not match, the user will be prompted to re-enter the encrypted number in the field labeled 'Verified Encrypted Number'. The purpose of this process is to ensure that the encrypted number transcribed from the screen to the Case Report Form accurately.

Medical Events [EVENTS]

Purpose: Ascertain if specific medical events related to kidney and cardiac disease have occurred over the course of study participation.

Who: Research Coordinator.

When: Completed at each clinic visit and telephone contact.

Directions: The RC will complete this questionnaire as an interview with the participant. Remind the participant of the date of the last CRIC Study contact.

Q1: Indicate if a doctor of HCP provided a diagnosis of heart attack, stroke or mini-stroke since the last CRIC Study contact.

Q2a-k: If YES to Q 2, each question regarding **hospitalization** requires a response.

Q2l: The RC determines number of separate hospitalizations, based on "Yes" responses by the participant on Qs 2a-2k. Be certain to ***confirm the number of separate hospital stays*** as some conditions may have occurred during the same hospitalization OR a participant could be hospitalized more than once for the same condition.

Q3: The RC should ask each question about tests/procedures in 3a – 3l. If any of the tests or procedures has been performed, the RC should indicate 'YES' to this question and indicate if the procedure occurred during an inpatient hospitalization or as an outpatient. Each question requires a response.

Q3m: The RC determines number of separate tests/procedures based on "Yes" responses by the participant on Qs 3a-3l. ***Confirm the number of separate tests/procedures*** since the last CRIC study contact.

Q4: If death is reported, indicate the name and/or relationship to the participant.

The RC should collect as much specific information about the date(s) and location of all hospitalizations, tests/procedures, treating or ordering physician, or death.

IMPORTANT NOTE: This information will initiate the next step in the event investigation process so it is imperative to collect complete and accurate information at this time.

EVENTS data will be entered and verified in the Data Management System (***DMS***). The text information in Q5 will not be entered in the DMS.

Kidney Disease and Quality of Life Questionnaire [KDQOL]

Purpose: Assess participant's quality of life and rate kidney-specific health issues.

Who: Participant, as a self-report.

When: Completed at Baseline Visit (Visit #3),
12-month follow-up (Visit #5),
24-month follow-up (Visit #7),
36-month follow-up (Visit #9),
48-month follow-up (Visit #11), and
60-month follow-up (Visit #13).

Directions: Kidney Disease and Quality of Life Questionnaire is a self-report. The participant should be instructed to read the instructions carefully at the start of each group of items. The participant should be instructed to check one response per item, and to also note that some items are time-limited (4 weeks).

The RC will check responses for completion and legibility.

If the questionnaire is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

KDQOL data will be entered and verified in the Data Management System (***DMS***).

Laboratory Results – CBC [LABCBC]

Purpose: Record CBC results, based on site-specific (local) laboratory report.

Who: Research Coordinator.

When: Completed at Baseline Visit (Visit #3),
12-month follow-up (Visit #5),
24-month follow-up (Visit #7),
36-month follow-up (Visit #9),
48-month follow-up (Visit #11), and
60-month follow-up (Visit #13).

Directions: These results are obtained from blood drawn and sent to the site-specific (local) laboratory. The RC should transfer the results from the lab report to this form.

Original copies of the laboratory report must be maintained in source documentation folders.

Any copies sent to the SDCC at their request must have participant information obliterated and the copy identified by PTID, PT Initials and Visit Number only.

LABCBC data will be entered and verified in the Data Management System (***DMS***).

Medical History Form [MEDHX]

Purpose: Collect relevant participant history in areas of general health, renal, cardiovascular, diabetes, social history and brief family history.

Who: Interviewer or participant, as a self-report.

When: Completed at Baseline Visit (Visit #3),
12-month follow-up (Visit #5),
24-month follow-up (Visit #7),
36-month follow-up (Visit #9),
48-month follow-up (Visit #11), and
60-month follow-up (Visit #13).

Directions: Instructions for completing the questionnaire must be reviewed with the participant. Some questions, where the participant may not be able to recall historical information, have the option of checking a "Don't Know" response. For all other questions, the participant must be encouraged to use his best judgment or estimate and respond. Responses to questions must not remain blank.

Medical terms have been simplified for use of ***MEDHX*** as a self-report, but the RC must be available to answer questions if the participant is unable to understand medical terminology.

The RC will check responses for completion and legibility. Special attention will be given to skip pattern responses when checking.

If the questionnaire is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

MEDHX data will be entered and verified in the Data Management System (***DMS***) as a single entry form.

Modified Mini-Mental State Exam [MMSE]

Purpose: Assess participant's cognitive function status.

Who: Research Coordinator.

When: Completed at Baseline Visit (Visit #3),
24-month follow-up (Visit #7), and
48-month follow-up (Visit #11).

Directions: Refer to the MMSE Manual in Appendix E for administering MMSE to the participant. Visual Aids have been distributed to the RCs.

Only data from the *MMSE Scoring Tally Sheet on page 9* of the form will be entered and verified in the Data Management System (*DMS*).

Participant Close-out (PTCL)

Purpose: Confirm that data collected for the CRIC study participant are correct, to the best of the PI and RC's knowledge.

Who: PI and RC completed.

When: 60 m follow-up/Visit #13 *or*
at premature termination.

General Directions:

PTCL ***must*** be completed for every participant at termination, whether at study completion or premature termination.

If this CRF is completed between scheduled visits, the RC will record the next Visit Number and the current date in the header.

PTCL will be entered and verified in the DMS.

Procedural or Unanticipated Problems [PUP]

Purpose: Record reportable problems associated with CRIC testing procedures.

Who: Research Coordinator/PI.

When: Completed as needed when a participant reports problems during or after administration of a CRIC medical/research procedure.

Directions: This CRF is completed on an "as-needed" basis *only*. Data is only recorded if the participant experiences problems related to any study procedures.

PUP must be completed and data-entered within 72 hours of the first report of study-related problems during, e.g. blood draw for laboratory testing, GFR testing-related problems. The RC will share this information with the CRIC PI and study staff at his/her site and report the incident(s) to the site's Institutional Review Board (IRB), according to their institutional reporting guidelines. The SDCC will generate PUP reports for the Sponsor, NIDDK, at predetermined intervals.

The CRF allows 2 reports to be recorded per page. If more than 2 incidents at a specified visit occur, additional pages are available. Reports are visit-specific. The RC should record the visit date associated with the problematic procedure in the CRF header, regardless of when the site is first notified of the incident.

Alpha-numeric PUP codes have been provided on the CRF for easy reference. 3-character codes identify the process and 2 digit sequential codes, separated by a separator, identify the most common problems that are likely to occur during the process. There are no known procedural problems associated with Ankle Brachial Index, Electrocardiogram, etc., but they have been listed for any unanticipated occurrences, should the need arise to report an incident.

Q1-1a: Since PUP is developed as an "as-needed" CRF, Q1 will always be answered as "Yes."

The "Yes" response will trigger the Data Management System to generate corresponding number of records to report the problem(s) after entering a numerical value in Q1a, which identifies the number of reported problems.

Problem *#:* This is a sequential number, starting with 1 (one) for the Data Management System to identify records.

PUP Codes: PUP codes are provided on the CRF.

Treatment for PUP: Treatment must to be provided or prescribed by a health care provider to be coded as "Yes."

Comments: This section allows the RC to record a brief description (25 words or less) for problems reported for processes that are not known to cause problems (unanticipated), e.g., ABI, BIA.

Additional incidents are recorded on ***PUP - Additional Page,*** available in the CRF module of the Data Management System *(DMS).*

PUP data will be entered and verified in the ***DMS***.

Physical Activity [PHYACT]

Purpose: Assessment of physical activity by the participant.

Who: Participant, as a self-report.

When: Completed at Baseline Visit (Visit #3),
24-month follow-up (Visit #7), and
48-month follow-up (Visit #11).

Directions: The instructions must be reviewed with the participant.

The RC will check responses for completion and legibility. Special attention will be given to skip pattern responses when checking.

If the questionnaire is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

PHYACT data will be entered and verified in the Data Management System (***DMS***).

Symptoms List [SXLIST]

Purpose: Record severity of kidney disease-related problems experienced by the participant.

Who: Participant, as a self-report.

When: Completed at Baseline Visit (Visit #3),
12-month follow-up (Visit #5),
24-month follow-up (Visit #7),
36-month follow-up (Visit #9),
48-month follow-up (Visit #11), and
60-month follow-up (Visit #13).

Directions: Symptoms List is a self-report. Instruction must be reviewed with the participant. The participant must have experienced the symptoms in the past month.

Severity is defined as:
Mild = Symptoms did not interfere with usual activities

Moderate = Symptoms interfered somewhat with usual activities

Severe = Symptoms were so bothersome that usual activities could not be performed

Q.24: Symptoms other than the one ones listed from item #1 through item #23 will be noted as "Other" in item #24, with a brief description.

If the questionnaire is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

The RC will check responses for completion and legibility.

SXLIST data will be entered and verified in the Data Management System (***DMS***).

Withdrawal [WITHDR]

Purpose: Document termination of a participant from the CRIC Study after cohort and sub-Cohort assignment, or at completion of 60-month follow-up.

Who: Research Coordinator.

When: Completed at 60-month follow-up (Visit #13) or when the participant prematurely withdraws from CRIC Study and/or sub-Cohort.

Directions: If the participant completes CRIC Study up to the 60-month follow-up phase, he/she is considered a study "completer." If the participant withdraws at any point prior to the 60-month follow-up visit (Visit #13), it is considered a pre-mature withdrawal.

Q.1a: A primary reason for withdrawal will be selected from the following categories:

- Ineligible at screening visit; does not meet eligibility criteria for enrollment
- Ineligible at baseline visit; does not meet eligibility criteria for enrollment
- No longer willing to follow the protocol; has concerns about the research processes in the CRIC Study; may not want to be subjected to repeated tests, blood draws, other processes; confidentiality or privacy issues
- Lost to follow-up; does not respond to repeated efforts to continue with follow-up contacts or visits by mail, phone
- Participant has personal constraints; e.g. unable to make visits during clinic hours, access to clinic is difficult
- Deceased
- Has reasons other than the above mentioned reasons; a brief description of the reason will be included

Q.1b: Participants who withdraw prematurely will have the option of withdrawing specimen stored for future analysis. They may choose to withdraw all or specific types of specimens. It is the responsibility of the RC to review the option with the participant. If possible, a written request is preferred for discarding stored specimens.

Q.1c: Completed for participants who withdraw prematurely.

Q.2: Date recorded for all participants.

Space is provided for additional comments

WITHDR will be entered and verified in the Data Management System (***DMS***).

5.A.2.(e). General Instructions for Administrative Case Report Forms

Administrative CRFs are optional in most situations but it is strongly recommended that they are used as a quality control measure for data collection. They can be included in the participant's study folder as a reminder of forms to be completed at each visit.

5.A.2.(f). Specific Instructions for Administrative Case Report Forms

Pre-Screening Administrative Case Report Forms

Health Data Review Form [HDREV]

Purpose: Initial review of a potential participant's data available through the site or Primary healthcare provider's medical records to determine general study eligibility, based on broad inclusion/exclusion CRIC Study criteria.

Who: Research Coordinator/chart reviewer.

When: Completed *prior* to Prescreening Visit (*Visit #1*); does not involve direct contact with the participant.

Directions: Items for which information is not available in the medical record may be left unanswered.

Source Information: Record the source from where the information was recorded on this CRF. Multiple sources can be used for data review.

Q.4: Multiple responses can be checked to determine participant's racial background.

Q.5: Serum creatinine value may be available in the participant's medical chart.

Q.5b: The eGFR calculator is available on the CRIC Study website and in the DMS. GFR is determined by using the serum creatinine value without applying the correction factor.

Q.6: Diagnosis of diabetes mellitus should have been given by a healthcare provider.

Q.7-20:"Not apparent" response is checked if the medical chart does not contain the information sought. Screening information that becomes subsequently available will allow the RC to determine a participant's eligibility. If response to any of the exclusion criteria is checked "Yes", the participant should not be considered for further screening.

Outcome: If the participant's chart does not indicate criteria that may possibly exclude him/her, the RC can arrange for the participant to be contacted for Prescreening Contact (Visit #1).

This CRF contains confidential participant information and will not be shared with the SDCC. It will be maintained and filed in a confidential folder and stored in a locked cabinet.

HDREV data is **not entered** in the Data Management System (DMS).

Healthcare Provider Contact information [HPCONT]

Purpose: Maintain contact information on participant's healthcare provider(s).

Who: Research Coordinator.

When: Completed at Screening Visit (*Visit #2*) and updated at each telephone contact and clinic visit.

Directions: Healthcare provider also includes primary care physician. Attempt will be made to maintain comprehensive information on participant's healthcare provider and update the information periodically.

If this information changes since the last visit or contact, complete a new CRF.

A checked box indicates the participant has consented to share his/her medical information with the healthcare provider.

This CRF contains confidential participant information and will not be shared with the SDCC. It should be maintained and filed in a confidential folder.

Prescreening Visit Checklist/Progress Notes [PRESCRCL]

Purpose: Provides a list of processes and corresponding CRFs and supplies needed for the Prescreening Visit (Visit #1). PRESCRCL can be considered as source documentation for the visit.

Who: Research Coordinator.

When: As a reference tool/source documentation, to be used at Prescreening Visit (Visit #1).

Directions: This CRF is a reference tool for the Research Coordinator (RC) to complete study procedures at Prescreening Visit (Visit #1). Materials and supplies needed at the visit are listed at the top of the page. Processes to be completed at the visit are also available as checkboxes, as a reminder to the RCs.

PRESCRCL will be updated each time an amendment is made for the visit.

Participant Contact Information [PTCONT]

Purpose: Maintain participant's information to facilitate periodic follow-up contacts.

Who: Research Coordinator.

When: Completed at Screening Visit (*Visit #2*) and updated at each telephone contact and clinic visit.

Directions: Attempt will be made to maintain comprehensive contact information on the participant and update the information periodically.

If this information changes since the last visit or contact, complete a new CRF.

This CRF contains confidential participant information and will not be shared with the SDCC. It should be maintained and filed in a confidential folder.

Prescreening Script [SCRIPT1]

Purpose: Disseminate information about the CRIC Study to participant at the Prescreening Contact in a consistent manner; use to obtain verbal consent from the participant to collect prescreening information.

Who: Research Coordinator.

When: Used at Prescreening Visit (*Visit #1*) only.

Directions: This site-specific script will be used to introduce the caller and inform the participant about the CRIC Study. Space is provided at the end of the script to document participant's consent.

This script precedes the Prescreening Information (PRESCR) CRF.

This script contains confidential participant information and will not be shared with the SDCC. It will be maintained and filed in a folder along with the signed Informed Consent for enrolled participants, separate from the participant's research data.

Prescreening-Exclusion Script [SCRIPT2]

Purpose: Provide a tool for the Research Coordinator when excluding a potential participant at prescreening visit, by answering their questions with sensitivity and consideration.

Who: For the Research Coordinator.

When: Used at Prescreening Visit (*Visit #1*) only.

Directions: When the participant is not considered qualified for participation, he/she may have questions about why he/she can't participate. The research coordinator must use tact and sensitivity in declining the participant without revealing the specifics of the study criteria. SCRIPT2 provides guidelines for the research coordinator to gently explain the reason for excluding the participant.

This script is used in conjunction with the Prescreening Information (PRESCR) CRF.

Study Administrative Case Report Forms

Administrative Case Report Forms List [ACRFLIST]

Purpose: List of administrative CRFs with CRF code names, and the latest version numbers.

Who: For the Research Coordinator.

When: As a reference tool at any point during the CRIC study.

Directions: This CRF is a reference tool for the Research Coordinator (RC) to maintain current the version of the CRFs to be used for the study

ACRFLIST will be updated each time a CRF on the list is updated and the RCs will be alerted to the update.

Baseline Visit Checklist/Progress Notes [BASECL]

Purpose: Provides a list of processes and corresponding CRFs and supplies needed for the Baseline Visit (Visit #3). BASECL can be considered as source documentation for the visit.

Who: Research Coordinator.

When: As a reference tool/source documentation, to be used at Baseline Visit (Visit #3).

Directions: This CRF is a reference tool for the Research Coordinator (RC) to complete study procedures at Baseline Visit (Visit #3). Materials and supplies needed at the visit are listed at the top of the page. Processes to be completed at the visit are also available as checkboxes, as a reminder to the RCs.

BASECL will be updated each time an amendment is made for the visit.

Comments Sheet [COMM]

Purpose: Record any relevant information for a visit or a CRF. It can be attached to the CRF or used to record "Progress Notes" for a visit.

Who: Research Coordinator/Principal Investigator.

When: Completed on an "as-needed" basis.

Directions: Multiple pages can be attached to note additional comments at a visit or to accompany a CRF.

Data Case Report Forms List [DCRFLIST]

Purpose: List of data CRFs with CRF code names, and the latest version numbers.

Who: For the Research Coordinator.

When: As a reference tool at any point during the CRIC study.

Directions: This CRF is a reference tool for the Research Coordinator (RC) to maintain current the version of the CRFs to be used for the study

DCRFLIST will be updated each time a CRF on the list is updated and the RCs will be alerted to the update

Data Processing Cover Sheet [DPCS]

Purpose: Maintain record of data review and entry at each visit.

Who: Research Coordinator/Data entry personnel.

When: Completed at each clinic visit and telephone contact involving data collection and data entry.

Directions: The RC will check the box for the contact or visit for which the DPCS is completed. RC and/or data entry personnel will initial and date when review and entry functions are completed.

Participant ID Log [PTIDLOG]

Purpose: Assign participant ID number to participants who are contacted for the purpose of completing the Prescreening Contact CRF, regardless of whether they qualify for the Cohort.

Who: Research Coordinator.

When: Prior to the Prescreening Contact.

Directions: Every participant who is addressed to complete the Prescreening Contact is listed on the PTIDLOG and given a Participant ID number (PT ID) which will be used for identifying the participant for the remainder of his/her contact with the CRIC Study.

PT ID once assigned cannot be deleted or re-used for another participant.

Screening Visit Checklist/Progress Notes [SCRCL]

Purpose: Provides a list of processes and corresponding CRFs and supplies needed for the Screening Visit (Visit #2). SCRCL can be considered as source documentation for the visit.

Who: Research Coordinator.

When: As a reference tool/source documentation, to be used at Screening Visit (Visit #2).

Directions: This CRF is a reference tool for the Research Coordinator (RC) to complete study procedures at Screening Visit (Visit #2). Materials and supplies needed at the visit are listed at the top of the page. Processes to be completed at the visit are also available as checkboxes, as a reminder to the RCs.

SCRCL will be updated each time an amendment is made for the visit.

Participant Transfer [TRANS]

Purpose: Notify the SDCC and the Receiving site when a participant transfers from one site to another during the CRIC Study follow-up phase.

Who: Research Coordinator.

When: When a participant transfers to another site.

Directions: The Originating site completes page 1 of this CRF and includes a copy of TRANS with the participant's study binder, which is then mailed to the Receiving site. *A copy also should be mailed or faxed to the SDCC.*

The Receiving site completes page 2 of this CRF after receiving the required materials from the Originating site and the participant has signed the Receiving site's informed consent documents. ***A copy should also be mailed to the SDCC.***

A participant ***cannot*** be transferred to another site during the recruitment/enrollment phase of the CRIC Study.

Recruitment Chart [CHART 1]

Purpose: Provides information on processes and CRFs administered at the 3 recruitment phone contacts and/or visits.

Who: For the Research Coordinator.

When: Prescreening, Screening and Baseline Visits (Visits #s1, 2 and 3).

Directions: This CRF is a visual aid for the Research Coordinator when a potential participant agrees to the CRIC Study. This chart will be used as a check list to ascertain that all study processes have been completed for a contact or a visit for a potential participant during the recruitment process. Header information is provided to individualize the chart for each participant and will be maintained in the study binder.

Follow-up Chart [CHART2]

Purpose: Provides information on processes and CRFs administered during follow-up phone contacts and/or clinic visits.

Who: For the Research Coordinator.

When: Each follow-up visit.

Directions: This chart is a visual aid for the Research Coordinator when a study participant is scheduled for a follow-up contact or visit for CRIC Study procedures. This chart will be used as a check list to ascertain that all study processes have been completed for a contact or a visit for he participant at follow-up. Header information is provided to individualize the chart for each participant and will be maintained in the study binder.

5.A.2.(g). Submission of CRFs to the SDCC

The Clinical Data Management (CDM) division of the SDCC is responsible for monitoring all data associated processes. CDM may request copies of any completed CRF or visit packets for any study participants at any time during the course of the study. Copies of CRFs could be requested for several reasons, including data auditing and CRF completion review.

If a request is made:

- The site is responsible for making photocopies of all requested CRFs.
- The original CRFs should remain in the participant's study binder and the ***photocopies*** sent to the SDCC.
- All personal identifiers should be removed from the copies sent to the SDCC.
- All multi-page CRFs should be stapled and the visit packet should be paper-clipped.
- Preferably, copies should be sent to the SDCC via overnight mail.
- It is very important that response to requests be made as soon as possible, to ensure data quality.

5.B. Data Quality Management Procedures

5.B.1. Queries:

Queries will be sent to the Research Coordinators in response to errors logged by the Data Management System (***DMS***) when it views the verified data in the application against a set of rules, written to validate the data. A query can also be generated by a manual review of the verified data against an expected set of data standards, by the Data Management staff at the SDCC.

5.B.1.(a). Types of queries generated by the database

There are several types of queries sent to the sites that are generated by the DMS.

5.B.1.(b). Missing Fields

Collected data will be reviewed for completeness at the sites ***prior to*** entry and verification. A data field on a CRF that is left blank in the application will be logged as an error by the DMS and will be queried; e.g., if a medical history question was left blank, the RC can inform the SDCC (***in the same format as the query sent by the SDCC***) by e-mail of the missing field soon after the data is entered and verified or a query will be sent by the SDCC requesting the information.

If a query is sent to the site, the RC will attempt to find the correct response or provide an explanation. An explanation is acceptable when a response is left blank for a reason. For example, halfway through the participant's follow-up, the PI may request CBC but not differential. Therefore, when completing the ***LABCBC*** CRF, the data fields for Eosinophils, Basophils, Neutrophils, Monocytes and Lymphocytes will be left blank. When this is queried, the acceptable response to the query would be that these "tests were not ordered".

5.B.1.(c). Skip Patterns

Skip patterns account for fields that should or should not be answered, depending on the response to the first question in the series. For example, "types of cancer" for Question 1a on ***MEDHX*** CRF should only be answered if participant has been diagnosed in the past with cancer. If "types of cancer" is coded and the participant has not been diagnosed with cancer, a query will be sent because the field should be blank. Conversely, if the participant was diagnosed with cancer and "types of cancer" has not been checked, a query will be generated because the field should ***not*** be blank.

If a skip pattern query is sent to the RC, and a change is warranted, the CRF with the correction should accompany the faxed response to the SDCC.

5.B.1.(d). Range Checks

Many fields have a specific range of expected responses, which is designed to include approximately 95% of the population. For example, a participant's height has both a low range and a high range, and anything outside of those ranges ***may*** generate a query. The range check query is sent to confirm the value entered because it is higher/lower than the expected range.

The RC should confirm data that is queried in his/her response to the SDCC. A copy of the CRF is not needed with the response.

5.B.1.(e). Logic Checks

These checks review the data to ensure the data is logical, e.g., men should respond "NA" to female-oriented questions, and women should respond "NA" to male oriented questions.

5.B.2. Types of queries generated by manual monitoring

5.B.2.(a). Monitoring Checks

These checks monitor the data for completeness and accuracy. Data Management staff at the SDCC will manually view the data and queries will be sent for data that looks incomplete or appears to conflict with the design of the study. The Research Coordinators will manage these queries in a similar manner as outlined above for the database-generated queries. If changes are necessary, a faxed response with the corrected CRF will be expected. An explanation, without data change, can be sent by e-mail. Types of monitoring queries include:

- **Safety issues** – ALERTs, CMED, EVENT, GFR, PUP, and LAB related coding issues.
- **Study Procedures** – Withdrawal, Data Entry and Verification Status.

5.B.3. Managing Queries

5.B.3.(a). Receiving Queries from CDM

1. Queries will be sent via email, and will contain the following information:
    - CC ID
    - Site
    - Participant ID
    - Participant Initials
    - Visit Number
    - CRF Name
    - CRF Date
    - RC ID
    - Date Queried
    - Description of the Problem
    - The e-mail subject line of each query identifying an electronically generated query (Query – Participant ID/Visit Number/CRF name) or a monitoring query (Monitoring Query – Participant ID/Visit Number/CRF name).
    - The subject line indicating the query as a second or third attempt at seeking response from the site (Second Query – Participant ID/Visit Number/CRF name).

5.B.3.(b). Making Corrections Based on Queries

- The RC will print all queries e-mailed by the SDCC. At sites with more than one RC, the lead RC will inform the SDCC at the start of the study how they would like to receive the queries – whether one RC at the site receives all queries or the RC ID on the CRF determines who receives the queries.
- The RCs will be responsible for identifying the correction to be made or providing an explanation. SDCC Data Management staff will be available to assist the RCs in resolution of the queries, if needed.
- If a query results in a correction, the correction must be included on the query and documented on the original CRF (initialed and dated).
- If it is determined that a correction is not needed, an explanation (e.g. test not done, participant's height is correct), should be documented on the query.
- All queries should be initialed, dated and filed with the participant's data binder.
- Any questions related to the queries should be directed to the originator of the query at the SDCC.

5.B.3.(c). Query Response to the SDCC

- Queries can be returned to the SDCC via email ***or*** fax. A copy of the response e-mailed or faxed to the SDCC is retained in the participant's study binder.
- Explanations that do ***not*** require changes to the database can be e-mailed to the SDCC.
- The response to the query should be directed to the originator of the query at the SDCC.
- ***Original text must be "quoted"*** if responding to the query by email.
- A dedicated fax line [(215) 573-4790] is available at the SDCC to accept query responses and data sent from the sites.
- Responses to safety-related queries are expected at the SDCC in 3 working days. Responses to all other queries are expected at the SDCC in 5 working days.

5.B.4. Managing Responses to Queries

Type of Query	Data Change Necessary	No Data Change/Explanation
Missing Fields	Response by email or fax	Response by e-mail; CRF not necessary
Skip Patterns	Response by email or fax	N/A
Range Checks	Response by email or fax	Response by e-mail; CRF not necessary

Logic Checks	Response by email or fax	Response by e-mail; CRF not necessary
Monitoring Checks	Response by email or fax	Response by e-mail; CRF not necessary

6. Managing Participant Data

6.A. Alerts

The purpose of defining medical alerts is to identify and report significant medical findings that arise during participation in the CRIC Study to the participant and his/her health care provider. Participants and their providers must be notified immediately if potentially serious medical problems are identified during any of the examinations. Urgent conditions will be reported as soon as possible after they become evident.

Immediate and urgent alert information is accumulated in the data management system [DMS] as lab, ECG and Echocardiogram results become available. Lab values are identified in the database as being present in a DMS module called LAB STATUS. The LAB STATUS module is a look-up table that indicates by ID # if lab values have been received and if alert values are present. A viewable lab report table is populated with lab values as they are transferred to the DMS. Alerts will be designated by a visual signal or flag. The presence of an alert requires the RC to acknowledge receipt of alert information by completing the appropriate case report form [ALERT - Immediate or Urgent] and completing the notification chain of communication by contacting the participant's health care provider. Documentation of this notification is also required on the ALERT CRFs.

6.A.1. Recognizing Alert Conditions

Immediate alerts are those associated with a medical emergency and require a prompt response. If study personnel cannot assess and manage an emergency situation, they must be certain to know where to find help. If this occurs during a participant's scheduled CRIC Study visit, you are obliged to react to the situation and document the occurrence later.

Identifying alert values based on laboratory or test results in the database depends on receipt of clinical information from CRIC Central Laboratories, local laboratories, ECG review by the investigator or designee and the ECHO Reading Center. Therefore, it is important to conduct study tests on schedule and to transfer samples or test recordings as soon as possible. It is important to note that this information is not intended to replace clinical assessment of an individual participant's health status. The CRIC Study is providing this as supplemental information to the medical attention that participants are receiving from their providers.

6.A.2. Types of Alerts

6.A.2.(a). Immediate Alert - Defined

- Immediate Alerts are medical emergencies such as systolic BP > 180, diastolic BP > 110, chest pain, severe respiratory distress, acute neurological symptoms. The following Echocardiogram findings are also considered immediate alerts: severe aortic stenosis, aortic dissection, vegetation, tumor, cardiac tamponade, LV thrombosis.

- Immediate alerts will be evaluated by a physician who will determine the appropriate disposition. Immediate notification of the participant's physician should be accomplished by telephone, **before the participant leaves the clinic**. A follow-up letter documenting the information discussed by telephone must also be sent to the participant's physician.
- Use the **Immediate Alert [ALERT_I] CRF** to document the event(s) and alert notification. NOTE: If the alert is also an identified medical event that requires further documentation and classification, complete the **EVENT CRF**.

The table below defines **Immediate Alert** situations. The actions defined in the table must be completed within the time described. In most cases, this is prior to the departure of the participant from the study environment.

FINDING	ALERT TYPE	RESPONSE TIME
Blood Pressure: ▪ Systolic BP > 180 ▪ Diastolic BP > 110	Immediate* or Urgent	*As assessed by clinical evaluation at the time of the BP measurement
Acute Distress including: ▪ Chest pain ▪ Severe respiratory distress ▪ Acute neurological symptoms ▪ Other signs or symptoms constituting an emergency	Immediate*	*As assessed by clinical evaluation at the time of the CRIC Study visit
Echocardiogram abnormalities identified by technician and/or reading center: ▪ Severe aortic stenosis ▪ Aortic dissection ▪ Vegetation ▪ Tumor ▪ Cardiac tamponade ▪ LV thrombosis	Immediate	▪ Local review by technician during procedure or within 24 hours ▪ Central reading within 8 weeks

6.A.2.(b). Reporting Immediate Alerts

Immediate alert events require notification to the participant's primary care physician or provider **prior to the participant's departure from the clinic or medical center.** This should be accomplished by telephone as soon as possible after the occurrence by the investigator or coordinator from the CRIC Study team. Write a short summary for inclusion in the participant's research/source document file and send a copy of the memo describing the event to the primary health care physician or provider. Fax followed by paper copy may be preferred. When this has been accomplished, this information should also be noted on the ALERT_I case report form. This indicates that important medical information has been transmitted to the participant's health care provider which is one of the intentions of the CRIC Study.

6.A.2.(c). Urgent Alert – Defined

Urgent Alerts are lab values or ECG findings that require prompt notification of a participant's primary health care physician or provider. 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. Urgent alerts require notification of the participant and primary care physician **within 24 hours of receipt** of the results at the clinical center.

Use the **Urgent Alert [ALERT_U] CRF** to document the lab value, ECG finding or blood pressure measurement that initiates alert notification. If the alert is one of the identified events that require documentation and classification, complete the **EVENT CRF.**

Whenever an **Urgent Alert** listed in the table below is identified, the actions defined below must be completed within the time described.

FINDING	ALERT TYPE	RESPONSE TIME
Laboratory Values: ▪ Potassium ≥ 6 mEq/L or ≤ 3.0 mEq/L ▪ Sodium <125 mEq/L or >155 mEq/L ▪ Total Bicarbonate <15 mEq/L or > 40 mEq/L ▪ Calcium <6.5 or >13.5 mg/dL ▪ Glucose < 50 mgdL or > 350 mg/dL ▪ Creatinine doubling from last value ▪ CBC Hb < 7 gm/dL	Urgent	Within 24 hours of receipt of report at clinical center
ECG Findings: ▪ Acute MI ▪ Bradycardia = Heart Rate < 45 ▪ Tachycardia = Heart Rate >120 ▪ Acute myocardial infarction or ischemia ▪ Ventricular tachycardia ▪ Atrial fibrillation ▪ Atrial flutter ▪ Mobitz Type II 2nd degree heart block ▪ 3rd degree heart block ▪ Complete left bundle branch block	Urgent	Local review by medical staff within 24 hours

6.A.2.(d). Reporting Urgent Alerts

Urgent alert events require notification of the participant's primary care physician or provider **within 24 hours of receipt of the information**. This should be accomplished by telephone as soon as possible after the occurrence by the investigator or coordinator from the CRIC Study team. A short summary should also be written in the participants' research/source document file and a copy of this memo or the lab result, if that is the alert being reported, must be sent to the primary health care physician or provider. When this has been accomplished, this information should also be noted on the ALERT_U case report form. This indicates that important medical information has been transmitted to the participants' health care provider which is one of the intentions of the CRIC Study.

6.B. Summary Reporting of CRIC Study Information

6.B.1. Reporting Procedures for Study Values

CRIC investigators and coordinators recognize the obligation and importance of reporting research information to the health care providers of participants and participants themselves.

1. Results Reported
   - As laboratory, physical measures, and other test results become available they will be sent to participants and their primary care physicians. Permission to forward this information will be obtained during the consent process at the time of study entry.
   - The following results will be included in the reports:
     - Height, weight, waist circumference, body mass index
     - BP measurements
     - Ankle brachial index (***to physician/health care provider only***)
     - Chemistry lab values (including metabolic panel and lipid profile)
     - CBC
     - Urinary protein total
     - Estimated GFR using the modified MDRD equation
     - ^{125}I-GFR ***(as available on subcohort participants)***
2. Baseline Reporting Procedure:
   - An **initial** report will be mailed from the site approximately one month after the baseline visit and will include results of the screening laboratory tests, serum creatinine and glucose. It will indicate that a participant has agreed to enroll in the study, their eligibility status, and selection for the subcohort tests.

- A **second** report will be mailed 4 - 6 months after the completion of the Baseline Visit and tests. This report may include ECHO, EBT, GFR and any outstanding laboratory results.
- Similar reports will be provided after the subsequent annual examinations. These will not be identical to the baseline report because all tests are not repeated annually.

NOTE: Timeliness in reporting findings is dictated by the multi-center nature of the study and its complexity. It is important to note that information from tests listed above may be less than the full complement received during tests performed for clinical evaluation.

6.B.2. Types of Reports

6.B.2.(a). Health Care Provider Baseline Report

Study Results – <Date of Visit>

MEASURE	RESULTS	RANGE	
		NORMAL	ABNORMAL
Weight (kilograms)			
Height (cm)			
Body Mass Index[1] (BMI)		25 or less	Overweight: more than 25 Obese: more than 30
Waist Circumference[1] (inches)		Men-less than 40 Women-less than 35	
Blood Pressure[2] (mmHg)			
Systolic		Less than 130	Higher than 130
Diastolic		Less than 80	Higher than 80
Heart rate (beats/minute)		<100	100 or higher
Ankle Brachial Index		0.90 – 1.0	Less than 0.90
Left			
Right			
Kidney Function Tests:			
Estimated Glomerular Filtration Rate (eGFR)	(ml/min/1.73m^2)		
Measured Glomerular Filtration Rate (I -GFR)	(ml/min/1.73m^2)	Age I-GFR 21 – 30 >86 31 – 40 >82 41 – 50 >80 51 – 60 >75 Over 60 >70	
Serum Creatinine	mg/dL	Male 0.8 – 1.3 Female 0.6 – 1.0	
Total Urinary Protein	mg/24 hours		

[1] Based on Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults. NIH Pub. No. 98-4083, 1998.

[2] Based on The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure May 21, 2003.

LABORATORY TESTS		RESULTS	RANGES		
				Low	High
Metabolic Panel	Sodium	mEq/L	Serum/plasma	137	145
	Potassium	mEq/L	Serum	3.6	5.0
			Plasma 0.1 <	serum range	0.7 < serum range
	Chloride	mEq/L		98	107
	Total Bicarbonate	mEq/L		22	30
	Urea Nitrogen	mg/dL	Serum Male	9	20
		mg/day	Female	7	17
	Glucose	mg/dL	Serum male	75	
			Female	65	110
	Calcium	mg/dL		8.4	10.2
	Phosphorus	mg/dL	Serum	2.5	4.5
	Magnesium	mg/dL	Serum	1.6	2.3
	Uric Acid	mg/dL	Serum Male	3.5	8.5
		mg/day	Female	2.5	7.5
	Total Protein	g/dL	Serum	6.3	8.2
	Albumin	g/dL		3.5	5.0
	Total Bilirubin	mg/dL		0.2	1.3
	Alkaline Phosphatase	U/L		38	126
	Aspartate Aminotransferase (AST)	U/L	Male	17	59
			Female	144	36
	Alanine Aminotransferase (ALT)	U/L	Male	21	72
			Female	9	52
Lipid Tests[3]:	Total Cholesterol	mg/dL	Desirable	< 200	
			Borderline	200 – 239	
			High	> 240	
	Triglycerides	mg/dL	Normal	< 200	
			Borderline	200 – 239	
			High	400 – 1000	
			Very High	> 1000	
	HDL Cholesterol	mg/dL		35	
	LDL Cholesterol	mg/dL			170
Complete Blood Count:	Hemoglobin	g/dL	Male	14	18
			Female	12	16
	Hematocrit	g/dL	Male	42	52
			Female	37	47
	RBC	million/uL	Male	4.3	5.9
			Female	3.5	5.5
	WBC	thousand/uL		4.5	11
	Eosinophils	cells/cu.mm		3	
	Basophils	cells/cu.mm		1	
	Neutrophils	cells/cu.mm		60	
	Monocytes	cells/cu.mm		4	
	Lymphocytes	cells/cu.mm		32	
	Platelets	thousand/uL		150,000	400,000
	MCV	fl		76	96
	MCH	pg		27	32
	MCHC	%		30	35
Other Tests:	Homocysteine	µmol/L	Fasting	4	12
	Intact Parathyroid Hormone	Pg/mL		10	65
	HbA1C	%		4.0	8.2

6.B.2.(b). Participant Baseline Report

The information contained in this report will be identical to that on the report sent to the participant's health care provider with the exception of the Ankle Brachial Index. It is recommended that a CRIC Study representative or provider include a personal note with this report.

[3] Based on the Adult Treatment Panel Guidelines (ATP) III. National Cholesterol Education Program, NIH Pub. No. 01-3305, 2001.

6.B.2.(c). Health Care Provider Follow-Up Report

This report will be similar to the baseline report, though it may vary with regard to physical measures performed and available laboratory results.

6.B.2.(d). Participant Follow-Up Report

This report will be similar to the baseline report, though it may vary with regard to physical measures performed and available laboratory results.

6.B.2.(e). Accompanying Educational Information to Health Care Providers

The objective for distributing educational materials to health care providers is to provide them with useful information that may assist them in the care of their patients without interfering in the process of care or relationship with their patients. Initially, to accompany the Baseline Report we will distribute the National Kidney Foundation Kidney Function Preservation Practice Tool which includes useful information about the estimated GFR values being reported. Over the course of the study we will assemble a library of appropriate materials for distribution, and replace them according to a schedule.

6.B.2.(f). Accompanying Educational Information to Participants

CRIC participants may not be familiar with the information contained on the Participant Baseline Report. We have developed 2 versions of "Frequently Asked Questions" that you may send with the Baseline Report. They differ in the amount and difficulty of information provided in description of CRIC Study tests. Over the course of the study we will assemble a library of appropriate materials such as this for distribution and replace them according to a schedule.

6.B.3. Generating a Report from the Data Management System

The ability to generate participant reports from the Data Management System [DMS] will be a selection on the main menu. As reports are comprised of information from many different data fields on several case report forms, generating a report will be dependent on data entry and verification of those case report forms, in addition to the transfer of electronic data from reading centers and laboratories. You will be able to view and print a report at any time. The report will be populated, which means updated with additional information, as it is received. This option can be selected from the menu in the Data Management System. Therefore, a report can be previewed as often as needed prior to printing it, while checking for all of the information that is expected. See Section 7 of this manual for additional information.

6.C. Reporting Procedural and Unanticipated Problems

As determined by the Investigator and Research Coordinator, "*unanticipated* problems involving risks to participants or others," including unanticipated risks due to study procedures, as listed below, will be considered *reportable events*. These events should be recorded on the

Procedural or Unanticipated Problems [PUP] Case Report Form and reported to individual IRBs in accordance to their specific guidelines and timelines.

6.C.1. Reportable Events

The PUP CRF will itemize the following reportable events and assign a standardized code number as indicated below, with each type of event.

Reportable Events Associated With:

- Blood Tests*: The following participant experiences should be recorded and reported:

  BLD-01 Presyncopal episode or fainting episode

  BLD-02 Severe hematoma

  BLD-03 Prolonged bleeding

  BLD-04 Infection at the needle insertion site

Mild pain and bruising during a blood test is a common anticipated risk listed in the informed consent and will not require reporting.

*The above criteria apply to any/all blood tests, including those associated with GFR testing.

- Glomerular Filtration Rate (GFR): minimal radiation risk must be included in the informed consent form and becomes reportable only if:

  GFR-01 An inadvertent administration of a dose of Iothalamate, greater than the prescribed dose, occurs

  GFR-02 Allergic reaction to Iothalamate

  GFR-03 A pregnant or breast feeding woman, excluded from this test per the study protocol, is inadvertently exposed to this test

  GFR-04 Fluid overload in association with GFR, per clinical assessment

  GFR-05 Symptomatic hypoglycemic event in diabetic participants undergoing GFR test

- Electron Beam Tomography (EBT): minimal radiation risk must be included in the informed consent form, and becomes reportable only if:

  EBT-01 A pregnant or breast feeding woman, excluded from this procedure per the study protocol, is inadvertently exposed to this test.

There are no *known* risks associated with the following study procedures.

BIA-01 Bioelectrical Impedance Analysis (BIA):

ECG-01 Electrocardiogram (ECG)

ECO-01 Echocardiogram (ECO)

ABI-01 Ankle Brachial Index (ABI)

However, any unanticipated risks to the participant due to these procedures should be recorded (under the associated PUP CRF code number) along with a *concise description* of the event.

For example, if during the ECG the research participant should fall from the table and fracture his arm, code the event as:

ECG-01 (per ECG-related code above) and include descriptive text such as "participant fell from the exam table during the ECG resulting in fracture of his left humerus."

If any 'unanticipated problem' falls outside of the codes listed above, the event should be coded as:

MIS-01 [Miscellaneous] Provide a concise description on the PUP CRF in the text lines corresponding to #15. For example, "the phlebotomist was stuck with the needle used to draw the participant's blood."

This aligns with the Regulation's mandate to report "risks to others."

The PUP CRF is a 'prn form' which means that is completed by the RC only as needed if any of the above incidents occur. If it is completed, it must be entered into the Data Management System. As it contains reportable information, it should be entered into DMS within 72 hours of first knowledge of this information. The SDCC will create a summary report of PUP at predetermined intervals.

7. Data Management System User Guide

7.A. Overview

Description

This chapter provides specific instructions on the use of the software application used to enter and verify data into the Chronic Renal Insufficiency Cohort (CRIC) Study Data Management System (DMS).

System Support

The Scientific Data Coordinating Center (SDCC) will provide technical and managerial support for certain aspects of the DMS. Computing support specifically related to the DMS will be provided to the sites by the SDCC help desk, which is described at the end of this chapter.

7.A.1. Logging In

Purpose: To allow access to the CRIC Study DMS system applications, including CRFs and reports.

Users: Data Management/Data Entry Personnel

- Research Coordinator

User Actions:

- URL and Log On to the DMS:
- URL: http://alpha.cceb.upenn.edu/crcu_html/cric.htm

Log on:

- Open the Main Menu using a Web browser.
- The page begins loading and a separate window (known as an applet) pops up.
- A message box appears, prompting the user to login.
- Enter *USERNAME* (assigned by the SDCC Help Desk support).
- Enter *PASSWORD* (assigned by the SDCC Help Desk support).
- System Security Note: Username and Password information must not be shared. The DMS tracks user actions based on this access information.
- Enter the Database name – cric.

- Press the CONNECT button.
- At this point, the CRIC Study Data Management System Menu appears. At the top of the screen on the bar above the title, the Username and time of log in is displayed.

7.A.2. CRIC Study Data Management System Menu

Purpose: To allow access to the DMS applications. This application allows entry of participant data into the DMS located at the SDCC and view registered participant data and entry status. It also allows access to the latest versions of the study CRFs and reports.

Users: Data Management/Data Entry Personnel

- Research Coordinator

User Actions:

Choose a menu option:

1. **Register Participant:**
   - Register a Participant into the DMS.
   - Data entry or verification cannot proceed on a participant unless a Participant ID is registered.
   - Requires Participant ID, Participant Initials, Clinical Center number and Site number.
2. **Prescreening CRF Entry:**
   - Allows entry of Prescreening Visit (*Visit #1*) data.
   - Requires Participant ID, Participant Initials, Clinical Center number, Site number, CRF date and RC ID.
   - Requires relevant entry of prescreening data.
   - Allows browsing to confirm data entry status.
   - Allows entered data to be viewed without edit.
3. **Screening CRF Entry:**
   - Allows entry and verification of Screening Visit (Visit #2) data.
   - Requires Participant ID, Participant Initials, Clinical Center number, Site number, CRF date and RC ID.
   - Requires all relevant entry and verification of screening data.
   - Allows browsing to confirm data entry status.
   - Allows verified data to be viewed without edit.
4. **Baseline and Follow-Up CRF Entry:**

- Allows entry and verification of Baseline Visit (Visit #3) data.
- Allows entry and verification of data collected at follow-up clinic visits and phone contacts.
- Requires Participant ID, Participant Initials, Clinical Center number, Site number, Visit Number, CRF date and RC ID.
- Allows browsing to confirm data entry status.
- Allows entered and verified data to be viewed without edit.
- Allows generation of calendar for participant follow-up visits and contacts.

5. **Calendar Tools for Scheduling:**
   - Generates participant-specific follow-up schedule to determine future visits and contacts, with a target date and a plus and minus 2 month window to initiate follow-up contact.
   - Generates site-specific follow-up schedule to determine participant visits and contacts for a specific time period (a specified month).
6. **Link to CRIC Web Site:**
   - Provides a hyperlink directly to the CRIC web site home page.
7. **eGFR Calculator:**
   - Allows entry of relevant data/values to calculate eGFR to determine participant eligibility.
   - Allows entry of Participant ID-specific or individual variables (obtained at pre-screening) to perform the calculation to determine participant eligibility.
8. **CCF IGFR Calculation:**
   - Allows results from GFR specimen analysis at Cleveland Clinic Foundation to be entered and made available to the SDCC for data analysis and to the sites.
   - Sites do not have access to this option in the Data Management System.
9. **Medication Reference Tool:**
   - Application used to cross-reference medication brand name with their generic equivalents.
   - Provides numeric and analyzable codes for each medication.
   - Requires Brand Name, Generic Name or Code Name of medication.
10. **Forms and Reports:**
    - Allows download of the latest versions of the CRIC Study CRFs to be used for data collection.

- Provides standard reports to be used for participant medical updates, Primary Care Physician medical updates, alert values, and other study-related reports.

11. **Cancel/Exit:**
    - Exits the CRIC Study Data Management System Menu.

7.B. Register Participant

Purpose: To allow registration of a new participant into the DMS. This is required prior to entering participant visit data.

Users: Data Management/Data Entry Personnel

- Research Coordinator

User Actions:

1. **Enter the Participant ID:**
    - Participant ID is an 8-digit number:
    - The first two digits of the Participant ID represent the Clinical Center (CC) number.
      The next two digits represent the Site number.
      The last four digits represent the sequential enrollment of participants.
    - An error occurs if less than or more than 8 digits or any non-numeric characters are entered.
    - An error message appears for duplicate Participant IDs.
2. **Enter Participant Initials:**
    - Participant Initials are 3 uppercase letters.
    - An error message appears if less than 2 or more than 3 letters are entered or any character that is not a letter is entered.
    - An error message alerts the user to duplicate initials in the system.
3. **Mandatory Fields (neither field may be left blank):**
    - Participant ID
    - Participant Initials
4. **Enter Clinical Center number:**
    - Enter the number or use the pull-down menu to select from the Clinical Center list.
    - After entering or selecting the number, the screen displays Clinical Center name in the text box on the right.

5. **Enter Site number:**
   - Enter the number or use the pull-down menu to select from the Site list.
   - After entering or selecting the number, the screen displays Site name in the text box on the right.
6. **Verify Participant Registration:**
   - When all fields are entered, click on the button marked "VERIFICATION".
   - The screen clears all visible data and prompts the user to re-enter participant information as described above.
   - If any data differs from first entry, an error message displays the first entry value and the second entry value and allows the user to select the correct response.
   - During verification, the same constraints are applied to the data fields as mentioned above for first entry.

7.C. CRF Data Entry and Verification

Purpose: To allow entry and verification of CRF data at specific visits into the CRIC database.

Users: Data Management/Data Entry Personnel

- Research Coordinator

User Actions:

1. **General Information:**
   - If a CRF has been previously entered, an error message indicates duplicate entry.
   - Entry screens mirror paper Case Report Forms.
   - For each entry screen, the header information in the upper right hand corner of the screen displays Participant ID, Participant Initials, Clinical Center number, Visit number, CRF date and RC ID.
   - Data recorded on the paper copy of the CRFs is entered into the corresponding DMS fields.
   - Data fields fall into the following categories:

     ALPHABETIC – letters of the alphabet (e.g. A-Z, a-z).

     NUMERIC – numbers, including integers and decimals (e.g. 0.0-9.9).

     ALPHANUMERIC – a combination of alphabetic letters and numbers

(e.g. a10pB).

CATEGORICAL – a defined list of values (e.g. 1 = male, 0 = female).

DATE – in the format of:
2-digit month
2-digit day
4-digit year, separated by a slash (e.g. 07/04/2003).

Leading zeroes must also be used, when appropriate.

TIME – 4 digit numeric field, representing time in a 24-hour cycle (00:00 – 23:59).

CHECKBOXES – allows clicking the box to add or remove a check, to indicate a value of 1 or null.

FREE TEXT – allows any combination of the above including spaces, special characters, and punctuation.

- If data entry does not meet the required range or specifications of the date field, an error message appears in the grey area at the lower left-hand corner of the application window.
- Upon completing data entry for each CRF, the **"**Save**"** button allows entered data to be saved.
- Data cannot be edited after it has been saved or committed. If verification entry is pending, data entry errors recognized from first entry can be corrected at second entry.
- Entered and verified data requires SDCC intervention to correct data entry errors, through clinic-initiated data change request.
- Entered/verified data that is not saved prior to exiting the DMS is lost and requires re-entry.

2. **Navigation:**
   - Multiple page CRFs can be accessed by using the appropriate navigation buttons (e.g. "Next Page", "Previous Page") at the bottom of the screen.
   - "Tab" key is used to advance to the next data field.
   - Checkboxes can be checked using the spacebar or using the mouse by placing the cursor on the checkbox.
     (Note: Generally a blinking cursor is not visible on the checkbox fields. Instead, the checkbox will be highlighted in color and a message appears in the bottom, left part of the screen, instructing the user).
3. **Verification:**
   - All fields are entered and verified unless specified on the CRF.

- Data entered at verification is compared to data from the first entry.
- If data entered on second entry is different from the first, an error message displays first entry value, second entry value, and provides the user an option to enter "Other" or a different value from the first and second entry.
- Choose the correct value after checking against the CRF and clicking on the appropriate button. If neither the first nor second entry value is correct, click 'Other' and enter the new value.
- An appropriate selection has to be made for verification to proceed.

7.D. Prescreening, Screening, Baseline and Follow-up CRF Entry

7.D.1. Specific Information:

Purpose: To allow entry of key variables and selection of CRFs for entry or verification for a specific visit.

Users: Data Management/Data Entry Personnel

- Research Coordinator

User Actions:

1. **Enter Participant ID:**
   - Participant Initials, Clinical Center number, and Site number will be crosschecked with the corresponding Participant ID in the registration table.
   - Once Participant ID is verified in the DMS, Participant Initials, Clinical Center number, and Site number fields will be populated by the system.
2. **Enter CRF date:**
   - This date may be the same as the Visit date.
   - Once the date is entered and the tab key is used to move to the next field, a message prompts the user to re-enter the date. This confirmation protects against data entry errors that require SDCC intervention to correct once the data is committed.
   - If CRF date must to be changed to reflect a different completion date, the "Clear All" button allows the header information to be altered for that visit/contact.
3. **Enter RC ID:**
   - Use the same RC ID as recorded on the prescreening CRF.
   - Once the RC ID is entered and tab key or enter key hit, a prompt will remind the user to re-enter the RC ID. This confirmation protects

against data entry errors that require SDCC intervention to correct once the data is committed.

- If RC ID must to be changed to reflect different study personnel involvement at a visit/contact, the "Clear All" button allows the header information to be altered for that visit/contact.

4. **Enter CRF Name:**
   - Abbreviated CRF name may be typed (as printed on the bottom right corner of each paper CRF, e.g. Prescreening Information CRF is identified as PRESCR) or the pull-down menu may be used to select the CRF, by clicking on the arrow.
   - Once selected, the full name of the CRF is displayed in the text window to the right of the field.
   - For certain visit-specific CRFs, the Visit number updates automatically. If that fails to happen, the Visit number, as recorded on the CRF (e.g. PRESCR Visit Number is 1), is manually entered.
   - Entered and verified data committed to the database, can be viewed by the authorized site study personnel for data entry errors or to respond to SDCC queries, by selecting the "View" option.
   - Data made available for viewing is not available for editing at the site. Requests to edit committed data should be sent to the SDCC, as described in Section 5B.

7.E. Prescreening CRF Data Entry Menu

Purpose: Allows entry (single entry only) of the Prescreening Visit/Contact CRF into the DMS.

Users: Data Management/Data Entry Personnel

- Research Coordinator

User Actions:

1. **Enter Key fields:** (header information as outlined in the previous section - Prescreening, Screening, Baseline and Follow-up CRF Entry)
2. **After entering the key fields:**
   - Click on "Enter CRF" button.
   - Enter data by navigating through the data entry screen using the "Tab" key.
   - If necessary, the "Next Page" or "Previous Page" buttons will help the user navigate between pages.
   - Clicking on the "Save" button stores entered data.

- Clicking on the "Exit" button allows the user to leave the data entry screen with or without saving. A message box provides the option of saving, if the user has not saved entered data prior to exiting.

3. "**Browse CRF Entry Status"** button allows the RC or the user to view entered data by visit number, visit date, if single or double entry, data entered by and date of entry. This is a useful tool to determine if CRFs are entered for a participant. A coding of "0" in the "Enter No" column indicates both entries have been completed. A coding of "1" indicates, only one entry was accomplished.

7.F. Screening, Baseline and Follow-up CRF Selection Menus

Purpose: Allows entry of CRFs for Screening Visit (Visit #2), Baseline Visit (Visit #3) and follow-up visits (Visit # 4-13).

Users: Data Management/Data Entry Personnel

- Research Coordinator

Users: Site personnel:

- Data Management/Data Entry Personnel
- Research Coordinator

User Actions:

1. **Enter key fields** (header information), as outlined in Section 7D (Prescreening, Screening, Baseline and Follow-up CRF Entry.)
2. "**Browse CRF Entry Status**" button in the Screening/Baseline/Follow-up CRF Selection menus allows the RC or the user to view entered CRFs by visit number, visit date, if single or double entry, data entered by and date of entry. This is a useful tool to determine if CRFs are entered for a participant and to identify which CRFs need to be verified. A coding of "0" in the "Enter No" column indicates both entries have been completed. A coding of "1" indicates, only one entry was accomplished.
3. **Entry Mode selection:**
   - **Entry**: To perform first entry of the data from the CRFs.
   - **Verification**: To perform verification or second entry of the data from the CRF.
   - **Edit**: For SDCC Data Management personnel use only.
   - **View**: To view data without editing capability at the sites and the SDCC.
4. **After clicking on "Enter CRF" button:**
   - Enter data by navigating through the CRF using the "**Tab**" key.

- If a CRF has been previously entered, a message appears indicating entry status. After acknowledging entry status messages, another CRF entry may be chosen.

  When certain CRFs need to be entered in a specific sequence, the system enforces this constraint. If a CRF is selected out of sequence, a message instructs the user of the sequence.

  If the CRF selection meets the DMS requirements for entry or verification, the system opens the entry screen for that CRF.

  For each entry screen, the header information in the upper right hand corner of the screen displays Participant ID, Participant Initials, Clinical Center number, Visit number, CRF date and RC ID.

  Data **cannot** be edited at the site after it has been saved. SDCC intervention is required for all changes to the entered and verified data.

5. After the last CRF has been entered and verified for the current participant, the entry process can be repeated for the next participant.
6. Clicking on the "**Exit**" button allows the user to leave the data entry screen with or without saving. A message box provides the option of saving, if the user has not saved entered data prior to exiting.
7. Clicking on the "**Save**" button stores entered data.

7.G. Participant Assignment (ASSIGN)

Purpose: Assign eligible participants to cohort and sub-cohort at Screening Visit (Visit 2).

Users: Research Coordinator

User Actions:

1. The DMS provides assignment information that is recorded on the paper CRF by the user.
2. Participants who meet eligibility based on age, eGFR value and inclusion and exclusion criteria on the Eligibility Assessment CRF (***ELIG***) are assigned to the cohort and sub-cohort by the DMS.
   - Select data for assignment is extracted from Demographics Information (***DEMO***), Eligibility Assessment (***ELIG***) and Screening Laboratory Results (***SCRLAB***).
   - If the required CRFs are not entered and verified, an error message alerts the user to complete data entry prior to assignment.

3. If the participant appears ineligible, a message displayed on the screen indicates reasons.
4. **To Assign participant:**
   - Select Screening CRF Selection Menu.
   - Select ***ASSIGN*** CRF.
   - Click on eGFR button for the DMS to display the eGFR value.
   - This value is recorded on the paper CRF in the space provided for item #1.
   - Record data values displayed for item #s 2, 3 and 4 on the paper CRF.
   - Re-enter data from the paper CRF for verification in the DMS for item #s 2, 3 and 4, by clicking on the "**Verification**" button.
     - To be eligible for the cohort, item #3 must be "Yes/1".
     - To be eligible for the sub-cohort, item #4 must be "Yes/1".
     - To participate in the study, item #3 MUST be "Yes/1" and item #4 may be "Yes/1" or "No/0".

IMPORTANT NOTE: Complete the paper CRF for participants who are NOT eligible based on the eGFR calculation. Retain this CRF in the participant CRF binder in the event this participant is re-screened at a later date. This information will also be saved in the DMS.

7.H. Calendar Tools for Scheduling

Purpose: Allows follow-up schedule to be generated for individual participants at Baseline Visit (Visit 3) as well as assist RCs to generate a list of follow-ups due in a specified time period (a specific month and year).

Users: Research Coordinator

User Actions:

1. **To generate participant schedule:**
   - Click on Baseline and Follow-up CRF Entry.
   - Enter key fields (header information) in Baseline and Follow-up CRF Selection Menu.
   - Select "Baseline Registration" or type "BASELINE" in the space next to "Available CRFs".
   - Click on "Enter CRF" button.
   - Enter Baseline Visit Date on the entry screen for first entry only. Verification is not required for this data field.

- Click on "Calendar Tools for Scheduling" button.
- Under "Calendar Tools Menu" click on "Follow-Up" schedule.
- Enter 8-digit Participant ID, Clinical Center number and Site number.
- The information entered generates a participant-specific follow-up schedule for each clinic visit and phone contact.
- Follow-up contact schedule displays Visit Number, Visit Type, Target Date and a First and Last Possible Date based on a pre-determined window before and after the target date, when the participant can be seen for follow-ups.
- Space is provided for the participant and the RC to write in the actual date when the participant was seen for the visit.

2. In order to generate a specific Site Schedule, Baseline Registration information must to be entered for each participant, as described above. If the participant is not registered at Baseline Visit, the DMS will not generate an accurate list if participants who are due for a specified month.
   - Click on "Calendar Tools for Scheduling" button.
   - Under "Calendar Tools Menu" click on "Clinical Center" schedule.
   - Enter Month and Year for which the site wished to generate follow-up information, in addition to the Clinical Center number and Site number in the space provided.
   - The information entered generates a site-specific follow-up schedule for the specified month.

7.I. eGFR Calculator

Purpose: This tool may be used as a calculator of the estimated Glomerular Filtration Rate (eGFR).

Users: Data Management/Data Entry Personnel

- Research Coordinator

User Actions:

1. **<u>Two possible ways to obtain an eGFR value:</u>**
   - Entering a Participant ID that has completed screening and registration.
   - Entering the Key Variables (Serum Creatinine, age, gender and race).
2. **<u>Entering Participant ID:</u>**
   - eGFR is calculated if Key Variables have already been entered and stored in the database at Visit 1 and 2. Specifically, the participant is registered and ELIG, SCRLAB, and DEMO are entered and verified.

- If the required data is available, the calculator looks up the necessary variables and displays the eGFR value.

3. **To calculate eGFR based on existing data:**
   - Click on the "eGFR Calculator" button from the "CRIC Study Data Management System Menu"."
   - Enter Participant ID.
   - Click on "Calculate" button.
   - The eGFR value is displayed in the box at the bottom of the window.
4. **Entering the Key Variables:**
   - eGFR value may also be obtained by entering the key data used for the calculation.
5. To calculate eGFR based on available key variables:
   - Click on the "eGFR Calculator" button from the "CRIC Study Data Management System Menu"."
   - Enter:
     Serum Creatinine Value
     Age
     Gender
     Race
   - Click on "Calculate" button.
   - The eGFR value is displayed in the box at the bottom of the window.

7.J. Medication Reference Tool

Purpose: To determine numeric codes for participant reported medications noted on Concomitant Medications (CMED) CRF.

Users: Data Management Personnel

- Research Coordinator

User Action:

1. Click on the "Medication Reference Tool" button in the DMS.
2. When the medication Reference screen comes into view,
   - Enter query criteria:
     To search by Brand name
     To search by Generic name
     To search by Drug name
   - Enter partial names for a more comprehensive list to choose appropriate medication code.

- Enter complete brand or generic name to narrow search for a known or "popular" drug.

3. Click on "Execute Query" and select the most representative coding for the reported medication.
4. If the site personnel are unable to locate a medication, SDCC/CDM personnel may be contacted to assist with determining the numerical coding.

7.K. Forms and Reports

Purpose: To access CRIC Study CRFs and reports

Users: **Principal Investigators**

- Research Coordinator
- Data Management Personnel

User Action:

Case Report Forms: CRFs can be accessed by clicking on the Case Report Forms button. CRFs are available as:

- Visit packets, which includes all data collection and administrative CRFs needed for the visit, and
- Individual CRFs, available as: Data entry CRFs, or Administrative CRFs

Reports:

- To be developed

7.L. Messages

Purpose: To assist with application operations.

Location:

- Status Messages: Displayed in bottom left of the application window.
- Dialog Boxes: Pop up in dialog boxes.

User Action

1. User should record all error messages that indicate problems communicating with the DMS and report them to the SDCC help desk.
2. User must acknowledge messages by clicking the "OK" button on the dialog box.

3. **Types of Messages:**

- Information Messages:
    - Data entry messages indicating CRF entry status, e.g. **"**RC ID xxxx may be incorrect !!" or "First entry must be performed before second entry."
    - Messages indicating the completion of application process status, e.g. "You have completed the data entry for this form !!" or "Saving or Editing data is not allowed. This entry is for VIEWING data only!!"
    - Data entry messages indicating data types and ranges for entry, e.g. "Birth Date must be in the range of 1900 - 2015 for year" or "Time format HHMM where HH value must be 00-23 and MM value must be 00-59!!"
    - Messages indicating number of choices in a list box, e.g. In the Blood Pressure CRF (***BP***), Question 4, "Arm Used" displays a list of choices in the list box below:
        1. Right
        2. Left
    - In the Demographic Information CRF (***DEMO***), Question 2, "What is your gender/sex?" displays a list of choices in the list box below:
        1. Male
        2. Female

- Warning Messages:
    - Messages requesting acknowledgement prior to exiting certain application processes. For example, in the Eligibility Assessment CRF (***ELIG***), Question 27 must be answered. If the response to Question 27 is left blank, the message displayed after the "SAVE" button is clicked says "Question 27 cannot be blank. Please provide an answer!!"
    - Messages requesting acknowledgement prior to deleting data, **e.g.** In the Procedural or Unanticipated Problems CRF (***PUP***), if the delete icon on top of the menu bar is clicked for one of the problems, the following message displayed says "Are you sure you want to delete this record ? Yes / No"

- Error Messages:
    - Messages indicating problems committing data to the DMS or receiving data from the DMS. This may be the result of problems with the DMS, application server, or problems with Internet connection. All problems should be reported to the SDCC

helpdesk. **e.g.**. "ORACLE error 40508: There is a physical database space problem. Please contact DBA or Help Desk or try later!!"

Problems with the Internet connection may be solved by:
Exiting all DMS applications
Closing all Web browsers
Reconnecting and logging on to the DMS.

- Messages denying access if user lacks privileges to access applications, **e.g.** "You are not allowed to select EDIT Entry Mode !! Please select First Entry or Second Entry mode or View mode !!" or "You are not allowed to access this module (CCF i-GFR Calculation)!!"
- Messages indicating use of certain invalid keys **e.g.** If you are in the View or Browse mode and you attempt to edit a data field, the message displayed on the screen says, "FRM-40200: Field is protected against update."
- Messages indicating the completion of application process status, e.g. "You have successfully completed data entry for this form. The data have been successfully saved in the database."

7.M. SDCC Help Desk

The SDCC Help Desk provides technical support to all study personnel using Data Management System (DMS) software developed and distributed by the SDCC. The Help Desk will answer questions concerning the operation of the DMS and will assist in resolving any issues that hinder the effective use of the DMS software.

Technical Support

The Help Desk will provide technical support related to problems and issues that may arise when working with the web based DMS.

The Help Desk will not be responsible for providing technical support for hardware and/or software that was not provided by the SDCC (e.g. word processors, spreadsheets, modems, printers, and hardware).

Assignment of DMS Accounts

A DMS account consists of a username and password that uniquely identifies a user. DMS accounts are required for a user to gain access to the data entry area, and are the primary means for ensuring data security and confidentiality. Therefore, it is critically important that all DMS accounts are kept secure and confidential and are not shared with anyone.

Note: The username and password used to access the CRIC Web site (http://www.cristudy.org/) is **not** your DMS username and password. Access to the CRIC Web site infers no access to the

CRIC DMS. You may reach the CRIC DMS through a link from within the CRIC Web site but will then be prompted for the DMS account username and password.

In addition to providing data security and confidentiality, DMS accounts provide a means to trace all database activities to individual user accounts.

To obtain DMS accounts, a Clinical Center or Site representative should notify the SDCC project manager of the requested user's name and provide a general idea of what functions the user will be performing in the DMS. The SDCC Project Manager will in turn notify the Help Desk of the new user request.

When a DMS account has been created, the Help Desk will contact the user with his/her account information.

When personnel leave the project, a representative from the Clinical Center or Site should contact the SDCC Project Manager immediately. The SDCC Help Desk will then take the necessary actions to deactivate that user's database account.

7.M.1. Procedures for Obtaining Help Desk Support

Study personnel can contact the SDCC Help Desk by telephone or e-mail.

Telephone Support

- The SDCC Help Desk can be contacted at (215) 573-4623.

When contacting the Help Desk, the caller will need to provide the following information:

- Name
- Study Name - CRIC
- Clinical Center or Site Name/Location

If SDCC Help Desk personnel are not available to take the phone call, the caller will be forwarded to voicemail. When leaving a voicemail message, the caller must provide the following information:

- Name
- Study Name - CRIC
- Clinical Center Name / Location
- Phone number
- Description of the problem and level of urgency (low, medium, high)

E-mail Support

- The SDCC Software Systems Help Desk can be e-mailed at: sshelpdesk@cceb.upenn.edu

When sending e-mail, the following information must be provided:

- Name
- Study Name - CRIC
- Clinical Center Name / Location
- Phone number
- Description of the problem and level of urgency (low, medium, high)

Help Desk Expected Response Time

Every effort will be made to respond to voicemail and/or e-mail messages as soon as possible. To facilitate a timely response, help desk personnel are equipped with pagers and will be paged when there is a new voicemail message.

When ever possible, the SDCC Help Desk will attempt to resolve the issue during the initial call. Occasionally, a problem may occur that requires additional interaction between the caller, the Help Desk, data management, and/or other software systems personnel. Client patience and cooperation is always appreciated during such periods. Our goal is to restore normal operations as quickly as possible.

Help Desk Availability

The CRCU Software Systems Help Desk is available during normal business hours 0800 – 1700 U.S. Eastern Time).

8. Clinical Center and SDCC Responsibilities

8.A. Clinical Centers' Responsibilities

Each clinical center/site is responsible for coordinating all activities required to achieve the goals of the study. The Research Coordinator (RC) plays an integral part in keeping the study on course; therefore, every effort should be made to retain members of the study team throughout the study. If an RC leaves the study, however, the Principal Investigator is responsible for hiring a replacement immediately to ensure overlap between the relevant individuals. The departing RC is responsible for training the replacement RC or other staff on issues concerning the study specific to the clinical site.

Each clinical center is responsible for screening, recruiting, enrolling and retaining a designated number of study participants. It is the responsibility of the clinical center study staff to assess their accrual, ensure participant confidentiality, maintain appropriate study documentation, enter and transfer data in a timely manner, and participate in the CRIC Study meetings and conference calls.

The success of the study depends heavily on the ability of the clinical sites to retain enrolled participants throughout their follow-up phase. Clinical site staff are responsible for maintaining participant interest. Potential ways of accomplishing this are:

- Emphasizing the advantage of having a dedicated RC available to answer calls.
- Making a dedicated phone line with voice mail available to study participants.

Each site is expected to manage the study with integrity, professionalism, and confidentiality and to adhere to all applicable federal regulations and Good Clinical Practice Guidelines. The RC is expected to provide the most complete and accurate data possible. The responsibilities of each Clinical Site RC include:

- Recruiting, screening, enrolling, and following participants throughout the course of the study
- Confirming eligibility of each participant based on the study criteria identified in the protocol
- Maintaining participant confidentiality and storing documents appropriately
- Performing data entry and verification of CRFs
- Adhering to study protocol and the MOP in the implementation of procedures and the acquisition of data
- Responding to queries regarding study information from the DCC in a timely fashion
- In-servicing staff at clinical site to the study protocol
- Maintaining approval from regulatory affairs board for each center / site as required

- Completing and submitting annual/final reports as required by local Institutional Review Board
- Enlisting aid of staff at clinical sites to assist with identification of potential participants
- Serving as liaison with study site and the SDCC.

Personnel

Specific study training and certifications are required for all Research Coordinators. Annual training session will be conducted to update personnel on protocol procedures and requirements. Research Coordinators and study associates who measure blood pressure and ECGs will be initially trained and certified, and must renew certification as required.

Institutional Review Board

It is the responsibility of the Principal and Co-Investigator(s) at each site to provide the Institutional Review Board (IRB) with all pertinent materials and Informed Consent documents. HIPAA Authorizations should be provided to the IRB, as required by site. Approval of the protocol, the informed consent form, and data collection forms/questionnaires must be obtained and forwarded to the University of Pennsylvania, SDCC before screening or enrolling participants. The Investigator also maintains the responsibility of initiating protocol re-approval, notification of protocol and/or consent form changes and termination of the study according to IRB requirements. The SDCC monitors submission and annual renewal of these documents.

Documentation

A Regulatory Binder will be maintained and updated by each clinical center containing all essential documents, according to Good Clinical Practice (GCP) guidelines, required for conducting a study. These documents include:

- Signature Pages of Protocol & Amendments (signed/dated by PI)
- CRFs and Questionnaires (blank copy of all implemented versions) **
- Informed Consent Forms (ICF) (IRB Approved Version(s) and DCC template)
- HIPAA Authorization Template (with corresponding submission/approval, if applicable)
- Submissions, Approval Letters or Waivers and Correspondence and Recruitment Materials (Approved by IRB)
- IRB Membership List or Federal-wide Assurance Number
- Laboratory Certifications/Laboratory Normals
- CVs of All Investigators
- Signature & Delegation of Responsibilities Log
- Training Documentation for Site Staff (ongoing)
- Manual of Procedures ** with Signature Page (signed/dated by PI)

- Study/Tracking Logs (without participants' names; screening log must be secured elsewhere)
- Study-Related Correspondence
- Miscellaneous

Note: Documents with ** noted may be stored outside of regulatory binder but made available upon request

Note to File: Documents outlined above may be stored in other/additional binders during the course of the study; however a "Note to File" should be placed in any section where this occurs as a reference for monitors and a reminder to replace documents at time of study termination.

Case Report Form Binder

Clinical centers will maintain a Case Report Form binder that contains all data collection forms, select administrative forms and laboratory specimen shipment tracking forms completed during the course of the trial for each participant. No participant identifiers other than participant ID number and participant initials should be contained in this binder.

Participant Confidential File

Each Clinical Center will maintain and routinely update a Participant Confidential File that contains all documentation collected to support and verify information contained on the data collection forms. This includes the following original source documents: participant signed informed consent, medical records, laboratory results, contact information, administrative forms not contained in Case Report Form Binder, notes, and correspondence. Participant study documents containing any participant identifiers beyond participant ID number and participant initials should be contained in this file. These files must be stored under secure conditions in accordance with applicable regulations and until written notice from the sponsor or SDCC is received.

In order to substantiate the integrity of data collected, the SDCC recommends that separate 'source' documents be filed in the participant's study record for the following information:

1. Signed/dated notation of when informed consent and HIPAA authorization were obtained (and if any questions were addressed)
2. Signed/Dated entries of any patient contact (phone or in person) which briefly summarize what occurred. For example: "Patient was seen in the office today for CRIC Baseline Visit by Study Coordinator/Investigator. The following tests were performed: BP, AB Index, etc."
3. Information related to inclusion/exclusion criteria. Example: If the CRF indicates by a checkbox that a woman is post menopausal; the source document should contain confirmation of this as follows: "Participant reported that she stopped menstruating 3 years ago."
4. All lab and test reports

Also, please note the following:

- CRF binders and source document files should not be copied routinely.
- Administrative forms are NOT required. They are intended for use by coordinators if they find them helpful in organizing their work.
- Participant completed CRFs [Diet Hx Questionnaire, Beck Depression, KD Quality of Life, etc.] do not require corresponding source documentation.

Study Confidential File (1 per clinical center)

Each Clinical Center will maintain and routinely update a Study Confidential File which contains Participant ID Assignment Log, a photocopy of all participant signed informed consents and all financial documents related to the study. Any additional study specific documents containing participant identifiers beyond participant ID number and participant initials should be contained in this file.

Record Retention

Investigators and/or Research Coordinators maintain, on-site, in an orderly fashion, for a proscribed period of time, and make available to the sponsor or the sponsor's representative, the following documents: the signed study protocol, amendments, informed consent documents, and approval letters from the IRB, CRFs, all primary source documentation, and all letters of correspondence. The SDCC maintains all study records for a period in accordance with their internal Standard Operating Procedures (SOP) and applicable regulations.

8.B. SDCC Responsibilities

The SDCC, located at the University of Pennsylvania, is responsible for the overall leadership regarding study design and conduct, as well as document control and distribution, study communications, data management and analysis. The SDCC is responsible for:

- Establishing a Data Management System incorporating a web-based data transmission system
- Assessing data quality and completeness throughout the study
- Providing general assistance to the Clinical Centers to maintain long-term participation of the cohort study subjects
- Arranging meetings and conference calls of the Steering Committee, External Advisory Committee and various study related sub-committees
- Performing other administrative functions, including the preparation and distribution and updates of study protocol and manual of procedures necessary to coordinate the efficient operation of the collaborative study group

The SDCC also performs analyses as suggested by the Clinical Centers, Central Laboratories and Central Reading Centers, as well as development of tracking and storage procedures for laboratory samples, and proposes original analyses to the collaborative group for their

consideration. The SDCC prepares periodic reports on the progress of the study, including data quality control, and interim and final results to the Steering Committee, the NIDDK and the group of external advisors.

The SDCC has established, via subcontracts, Central Laboratories and Reading Centers, as deemed necessary by the study protocol. It provides administrative coordination for the Central Repository to be established and directly supported by the NIDDK, to store genetic material and other biological specimens obtained from cohort study participants.

The SDCC is responsible for the collaboration with study investigators in the analysis and publication of study results.

8.C. Personnel Training and Certification

The SDCC will conduct a personnel training session prior to study initiation. This comprehensive training session will include all aspects of the study protocol and Manual of Procedures (MOP) implementation such as staff-participant interaction, specimen handling, and data collection and entry procedures. Periodic conference calls and training sessions will be conducted to maintain standard application of procedures. All new personnel will be required to participate in a study training session. Retraining will occur on an annual basis.

8.D. Quality Control

The primary goal of Quality Control efforts in CRIC is to maintain as high a standard of data quality as is feasible within and among all clinical centers. Secondary and related goals are to quantify the quality of the data collected, to identify and document problems in data quality, and to provide feedback to the clinical center Investigators, Research Coordinators and staff so that corrective procedures can be made to minimize measurement error. These procedures include, but are not limited to:

- Developing a detailed, well-documented, standard process in the Manual of Procedures (MOP) that clearly describes all data collection procedures.
- Central training study personnel to perform the high-tech and more routine procedures in a standardized manner according to the MOP.
- Providing annual and ad hoc study personnel training on additional study procedures in accordance with current and revised versions of study protocol and the MOP.
- Developing certification requirements for all staff members prior to performing baseline study procedures.
- Developing and monitoring criteria for maintaining certification to perform procedures in CRIC throughout study duration.
- Implementing a process for the certification and maintaining certification requirements using checklists to evaluate technicians' performance and document that the necessary criteria are met.

Clinical Protocol and MOP Adherence

The SDCC will request and verify specific information from clinical and reading centers to ensure the application of study procedures as they apply to participant safety, required intervals for timely conduct of procedures, appropriate documentation of data and specimens and compliance with SOPs. This information will take the form of a written report and may be acquired during clinical site monitoring visits.

Clinical Site and Study Monitoring

The SDCC has developed written standard operating procedures (SOPs) to ensure that all aspects of the study are conducted in a standard and uniform manner. These procedures are organized into a Manual of Procedures (MOP), which complies with the protocol, GCP and applicable regulatory requirements. A data monitoring plan and schedule will be developed to assess protocol adherence.

Participant Accrual

The SDCC will produce summary participant accrual reports. These reports will detail ongoing participant involvement at study visit milestones throughout the study duration. Accrual reports will count the number of participants enrolled in the main cohort and the various sub-cohorts. These reports will be verified by each clinical center and discrepancies reported to the SDCC and distributed to the Clinical Center Principal Investigator, Executive Committee and the SDCC CRIC project team. If requested, these reports may be made available to the Data Safety Monitoring Board.

Database Auditing

A comparison of a certain percentage of data written on CRFs to that entered into the electronic database provides information that describes and quantifies the accuracy of the data entry process and use of the data management system by personnel at each clinical center. This information will take the form of a written report.

Database Administration and Network Security

The SDCC has Standard Operating Procedures established for authorizing and documenting secure access to the study website, documents and electronic Data Management System (DMS). These procedures ensure that only authorized personnel are able to view, access, and modify study data.

Data Reporting

A set of standard reports will be developed to describe study activities such as accrual, study progress, and data quality. These reports will be developed using ORACLE REPORTS and provided to Investigators, NIDDK and designated committees as appropriate.

Preparation and Integrity of Analysis Datasets: The SDCC Database Administrator will create a set of standard data access descriptor/view files, which will be used in the generation of

SAS analysis datasets. As datasets are extracted from the main study database, they can be utilized separately from direct database processing and thereby protect the integrity of the data.

9. Appendix A: Physical Measures

9.A. Collection of Nail Clippings

9.A.1. General Information

- Data collection of fingernail clippings will occur at baseline and annually for the duration of the CRIC Study.
- Record information on case report form – Nail Specimen [NSPEC]
- Specimen transfer case report form – Specimen Transfer – Cold Pack [TRANSCOLD]
- The nail clippers used must be 100% stainless steel to prevent metal contamination of the nail clippings.

Supplies: Neat Clipper available at:

VSO & A Marketing
169 Marion Street
Winnipeg, Manitoba, Canada
R2H OT3
Phone: 1-204-982-7211
Fax: 1-204-982-7219

Specimen storage container for the nail clippings:

Fisher brand sample vial with Hinged snap cap.
Opaque – 1.5oz (45mL)
Case of 600 available through the
Fisher Scientific Catalog - #03-341-75C

9.A.2. Instructions for Nail Specimen Collection

- Collection of fingernails is preferred. Toenail clippings are to be obtained only when participant cannot provide fingernail clippings.
- It is recommended that the participant provide the nail clippings during the clinic visit. If this is not possible, the participant can collect their clippings at home and mail them back to the CRIC clinical center by a specified date. The CRIC clinical center will provide the participant will a pre-paid envelope in which to mail the clippings back to the clinical center. Participants may have their nails clipped by a doctor, podiatrist, manicurist, etc, in advance of their scheduled clinic visit, and bring the clippings with them to the visit.
- Participant will be supplied with a 100% stainless steel nail clipper (Brand name: Neat Clipper) and a plastic specimen container in which to collect the nail clippings at each specified visit (use one container per visit).
- To minimize nail specimen contamination, participant will be instructed to only use nail clippers that are provided, and instructed to put the clippings into the plastic specimen container at the time of collection.

- Participant will be instructed to remove all nail polish prior to the clinic visit.
- During the clinic visit, each participant will clip their own fingernails. They are to clip all 10 fingernails. The amount of clipping obtained should be approximately one millimeter from each nail.
- Participant will place their fingernail clippings into the plastic specimen container and give the container to the study coordinator.
- If participant cannot provide fingernail clippings, they will be instructed to clip their toenails to obtain the required specimen. They will place the toenail clippings into the plastic specimen container and give the container to the study coordinator.
- The participant will be instructed to keep the nail clipper supplied for use during future annual clinic visit.

9.A.3. Storage of Nail Clippings

- The study coordinator will take the plastic specimen container that holds the participant's nail clippings and empty the contents into an opaque hinged snap cap specimen storage vial (Brand name: Fisher 1.5oz (45mL) opaque vial).
- Label the storage vial with the participant ID number, the visit number and the date of collection. *No other participant identifiers should be recorded on the vial.*
- Store the vial at room temperature in a dry environment at each clinical center.
- Complete the Nail Specimen (NSPEC) case report form for that clinic visit.

9.A.4. Additional Considerations

- It is preferred that participants do not wear nail polish on the data collection visit; however, painted nail clippings will be accepted.
- Acrylic nails are not acceptable. The participant should be asked to provide toenail clippings instead.
- Other nail treatments such as Nail Glue or Nail Strengtheners are acceptable.
- If the participant has his/her nails clipped by a doctor, podiatrist, etc., the participant may take the clippers and collection bag to their next visit.
- If the participant has nail fungus or discoloration, he/she may provide specimens unless the procedure causes pain or discomfort.
- If the participant cannot clip all ten nails, he/she should try to clip as many nails as possible. If the participant has very short fingernails and cannot clip at least one millimeter, we would prefer they take the clippings at home when the nails have grown. If the participant has a few long nails, they may clip a large amount of one nail, rather than a small amount of each nail. The participant should not clip both his/her fingernails and toenails in order to get a total of 10 nails.

9.A.5. Instructions for Shipping of Nail Specimens

- Periodic shipping of the nail specimens to the CRIC central laboratory will be conducted by the study coordinator.
- Indicate inclusion of the nail specimen on the Specimen Transfer **[TRANSCOLD]** form.

9.B. Anthropometric Measurements

9.B.1. Equipment:

Gulick II 150c anthropometric tape measure

Stadiometers: Quick Medical, Healthscales, Med-Electronics

Weight: platform digital scale, Health-o-meter

Record information on the case report form – Physical Assessment [PHYASSESS]

9.B.1.(a). Height:

Height is measured in conjunction with the weight measurement. It may precede or follow this procedure.

- A wall mounted stadiometer should be used that can be calibrated with a rod.
- Remove any hat, hair bows, or other head gear that would interfere with the top of the stadiometer touching the crown of the head.
- The participant should be in stocking feet or non-slip slippers and stand on a flat surface that is at a right angle to stadiometer. The weight is evenly distributed between both feet, and the arms are hanging by the sides with palms facing the thighs. The heels are together, touching the stadiometer. The feet are spread at a 60 degree angle to each other. Whenever possible, the head, scapula and buttocks should also be touching the stadiometer. The head is erect with eyes focused straight ahead.
- As the client inhales deeply, the horizontal board of the stadiometer is lowered to the most superior point on the head, compressing the hair. Standing height is measured to the nearest 0.1 cm.
- Two readings should be repeated.

9.B.1.(b). Weight:

A traditional balanced beam scale has been considered a reliable instrument for population measurement. In the past years, they have often been replaced by electronic digital scales, which are easier to operate. If digital scales are used, have the scale calibrated once a year by a reliable company. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material.

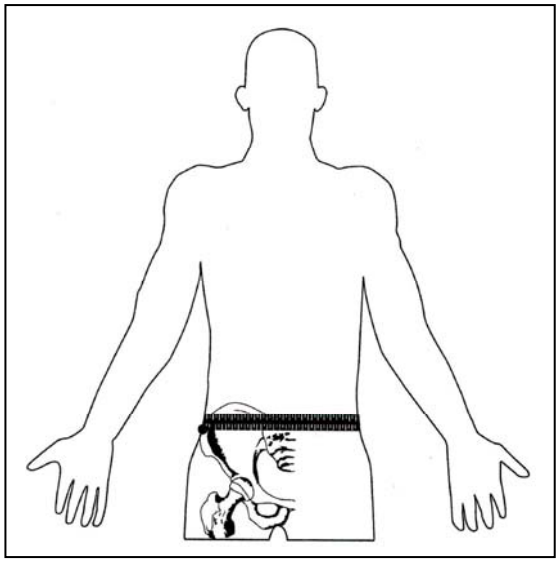
- Balance the scale so that the indicator is at zero.
- Participant should empty bladder.
- Participant should wear a hospital gown or light gym clothing, slippers and underpants.
- If the participant is too obese to stand securely on the scale's platform when looking straight ahead, he/she may stand sideways on the scale to take the weight measurement. Facing to the side rather than the front will provide the participant a wider base and more stability.
- Measure weight twice, having the participant step off the scale to repeat zero balance between measurements.
- Repeat if difference is greater than .1 kg.

- The scale should be calibrated per unit policy. If the scale is moved on a frequent basis, it should be calibrated more often. If it is stationary, the scale should be calibrated yearly by a certified scale calibration company.

9.B.1.(c). Waist Circumference

- Participant should be standing with arms held slightly away from the body
- Technician stands to the right side of the person. Locate the lateral border of the right ilium.
- Draw a horizontal line just above just above the uppermost lateral border of the right ilium and then cross the line to indicate the midaxillary line of the body.
- Standing to the right, place the Gulick II tape measure around the trunk in a horizontal plane at the level marked on the side of the trunk. Hold the zero end below the measurement value. Use the mirror to ensure correct alignment of the measuring tape.
- Using the Glick II tape measure, pull the end of the tape measure until two colored beads are seen. When you are pulling with exactly 4 ounces of force, you will see one of the colored beads; the other will be hidden behind the black casing. When you see one of the beads you are at the calibration point. The reading should then be taken.
- Each measurement should be done twice and be within 1 cm.

Abdominal (Waist) Circumference
National Health and Nutrition Examination Survey [NHANES]
Anthropometry Procedures Manual - Revised December 2000



To define the level at which the waist or abdominal circumference is measured, you must first locate and mark a bony landmark, the lateral border of the ilium. Have the participant stand and hold the examination gown above the waist. Lower the pants and underclothing of the participant slightly, and standing behind and to the right of the participant, palpate the hip area to locate the right ilium (see exhibit A). Draw a horizontal line just above the uppermost lateral border of the right ilium and then cross the line to indicate the midaxillary line of the body. Standing on the participant's right side, place the measuring tape around the trunk in a horizontal plane at the level marked on the right side of the trunk. Hold the zero end below the measurement value. Use the mirror on the wall to ensure correct horizontal alignment of the measuring tape. This is especially useful when measuring overweight participants or women with hourglass-shaped torsos. The recorder should also observe the participant to make sure that the tape is parallel to the floor and that the tape is snug, but does not compress the skin. Make the measurement at the end of a normal expiration and call it to the recorder to the nearest millimeter.

9.B.2. Resources for Assessment Tools

Stadiometers:
Quick Medical http://stadiometer.com/

Healthscales: http://healthscales.com
Med-Electronics: http://med-electronics.com/emed/itmidx14.htm
Steel Measuring Tape:
Gulick II http://www.fitnessmart.com/fitshopr/products/67020.htm

9.C. Ankle Brachial Index (ABI) Measurement

9.C.1. Background and Rationale

The presence of peripheral arterial disease (PAD) will be assessed with the ankle/brachial systolic blood pressure index (ABI). When the lower extremity arterial vasculature is normal, systolic pressures measured at the ankle level are slightly greater than or equal to brachial systolic pressure. Thus, a normal ABI is 1.0 to 1.3. When significant arterial stenosis occurs due to the development of atherosclerotic plaque, systolic blood pressure decreases distal to the stenosis. Progressively lower ABI values correspond to worsening arterial disease. However, this method may underestimate PAD in patients with medial arterial calcification and incompressible blood vessels, such as patients with long-standing diabetes and chronic renal failure.

9.C.2. Equipment and Supplies

- Doppler device with a continuous wave 8 mhz probe for vascular applications
- Ultrasound transmission gel
- Aneroid sphygmomanometer with a male quick release coupler. The manometer should be mounted at "eye level"
- Blood pressure cuffs: adult, large adult, and thigh
- Tissue or wash cloth to remove the ultrasound contact gel
- Black ball point pen and a marker
- Study records for documentation of ankle pressures, brachial pressures, and ankle-brachial index
- Record measures on the case report form – Physical Assessment [PHYASSESS]

9.C.3. Definitions

Peripheral arterial disease, peripheral atherosclerosis, and peripheral arterial obstructive disease are synonyms. Peripheral vascular disease may refer to venous disease, small-artery obstructive disease, vasospastic disease, cold sensitivity, or capillary disease and is thus not specific for the arterial system.

The ABI is a ratio of ankle to arm blood pressure and is computed separately for each leg. The numerator for the right leg is the higher of the two systolic ankle pressures (posterior tibial or dorsalis pedis) in the right leg. The numerator for the left leg is the higher of the two systolic ankle pressures in the left leg. The denominator for both legs is the HIGHER of the right and left brachial systolic blood pressures.

An ABI of 0.90 or less is considered positive for peripheral arterial disease, although peripheral arterial disease could exist if the ABI is 0.95 or less.

Mild disease is ABI <0.9 but ≥ 0.75. Moderate disease is ABI <0.75 but ≥0.50. Severe disease is indicated by an ABI <0.50.

Medial calcification could exist in an artery if the ankle systolic blood pressure exceeds 290 mm Hg in any participant, or 240 mm Hg in a participant with brachial systolic pressure less than 160 mm Hg, or if the ABI index is >1.3.

9.C.4. Method

1. Preparation for resting ABI measurement:
   - Conduct the examination in a quiet, warm, and comfortable room. It is important to carry out the measurements with the patients and their limbs comfortably warm to avoid vasoconstriction. The room temperature therefore should be between 24° and 26° C (or 75° and 79° F). If the room is cool, a blanket should be used to cover the participant.
   - Pressures are measured with the patient in the supine position after at least 5 minutes rest.
   - All pressure measurements are obtained with a continuous wave Doppler probe.
   - The arm pressure is measured before the ankle pressure. It provides the operator with some idea of the pressure that would normally be expected at the ankle.
2. Resting arm pressure measurement:

   The appropriate pneumatic cuff based on arm circumference should be used:

Arm Circumference	Cuff Size	
< 32 cm	**Adult**	**(12 cm width)**
32–42 cm	**Large adult**	**(17 cm width)**
≥ 43 cm	**Thigh**	**(20 cm width)**

   - The cuff is firmly wrapped around the upper arm, as high as possible, with the bladder of the cuff centered over the brachial artery.
   - Place a small amount of acoustic gel on the skin at the antecubital fossa (over the brachial pulse). Place the tip of the probe in the gel and in contact with the skin. The examiner's hand should rest gently on the patient's extremity to help steady the probe. Hold the probe so that it is "pointing up" the patient's arm at a 45° angle to the skin. The signal from the brachial artery will then be located by making very small and subtle adjustments in both position and angulation of the probe until the Doppler signal sounds strongest.
   - Steady the probe and maintain the audible Doppler signal as you inflate the blood pressure cuff with your opposite hand. Inflate the cuff to 20 mmHg above the pressure at which the Doppler arterial signal disappears.

- *Slowly* deflate the cuff at a rate of 2 mm Hg per second. Observe the manometer for the pressure at which Doppler sounds reappear. The first Doppler signal is the brachial systolic pressure. Fully deflate the cuff. Wait one minute if the measurement needs to be repeated.
- Repeat the same procedure on the other arm. After determining in which arm the pressure reading is higher, the operator will use the higher of the two values to calculate the ABI.

3. Resting ankle pressure measurement:

For each leg, complete the following steps:

- Wrap the adult (12 cm) blood pressure cuff around the ankle. Place the cuff so that the lower portion rests 3 cm above the medial malleolus (ankle bone).
- Obtain doppler signals from the Posterior Tibial Artery (PTA) and the Dorsalis Pedis Artery (DPA).
- The PTA pulse/Doppler signal is found medial and posterior to the medial malleolus.
- The DPA pulse/Doppler signal is found at the midpoint of the dorsal surface of the foot, in line with the space between the first two toes and the ankle.
- Place a generous amount of acoustic gel on the skin over the PTA. Place the tip of the probe in the gel and in contact with the skin. The examiner's hand should rest gently on the patient's extremity to help steady the probe. Hold the probe so that it is "pointing up" the patient's leg at a 45° angle to the skin. Slightly alter the probe angle to optimize the audible Doppler signal.
- Steady the probe and maintain the audible Doppler signal as you inflate the blood pressure cuff with your opposite hand. Inflate the cuff to 20 mmHg above the pressure at which the Doppler arterial signal disappears.
- *Slowly* deflate the cuff at a rate of 2 mm Hg per second. Observe the manometer for the pressure at which Doppler sounds reappear. The first Doppler signal is the brachial systolic pressure.
- If the signal remains faint as more pressure is released or if the probe moves off the artery, deflate the cuff completely, wait for 20 seconds, and then repeat the measurement.
- Place a generous amount of acoustic gel on the skin over the DPA. Repeat steps 3-5 above.
- NOTE: In a small percentage (< 10%) of participants, you will not be able to find the dorsalis pedis pulse.
- The higher of the two values (PTA or DPA) will be used to calculate the ABI in that leg.
- Calculate the ABI by dividing the higher of the 2 ankle pressures <u>in that leg</u> by the HIGHER (right *or* left) brachial systolic pressure:

$$ABI = \frac{\text{Higher of the two ankle systolic pressures}}{\text{Higher brachial systolic pressure}}$$

Example:

Blood Pressure: *(systolic only)*	
Right Brachial Pressure:	140 (mm Hg)
Right Dorsalis Pedis (DP) Pressure:	148 (mm Hg)
Right Posterior Tibial (PT) Pressure:	156 (mm Hg)
Left Brachial Pressure:	150 (mm Hg)
Left Dorsalis Pedis (DP) Pressure:	132 (mm Hg)
Left Posterior Tibial (PT) Pressure:	138 (mm Hg)
Ankle Brachial Index:	
Right AB Index:	[156 /150 = 1.00]
Left AB Index:	[138 / 150 = 0.92]

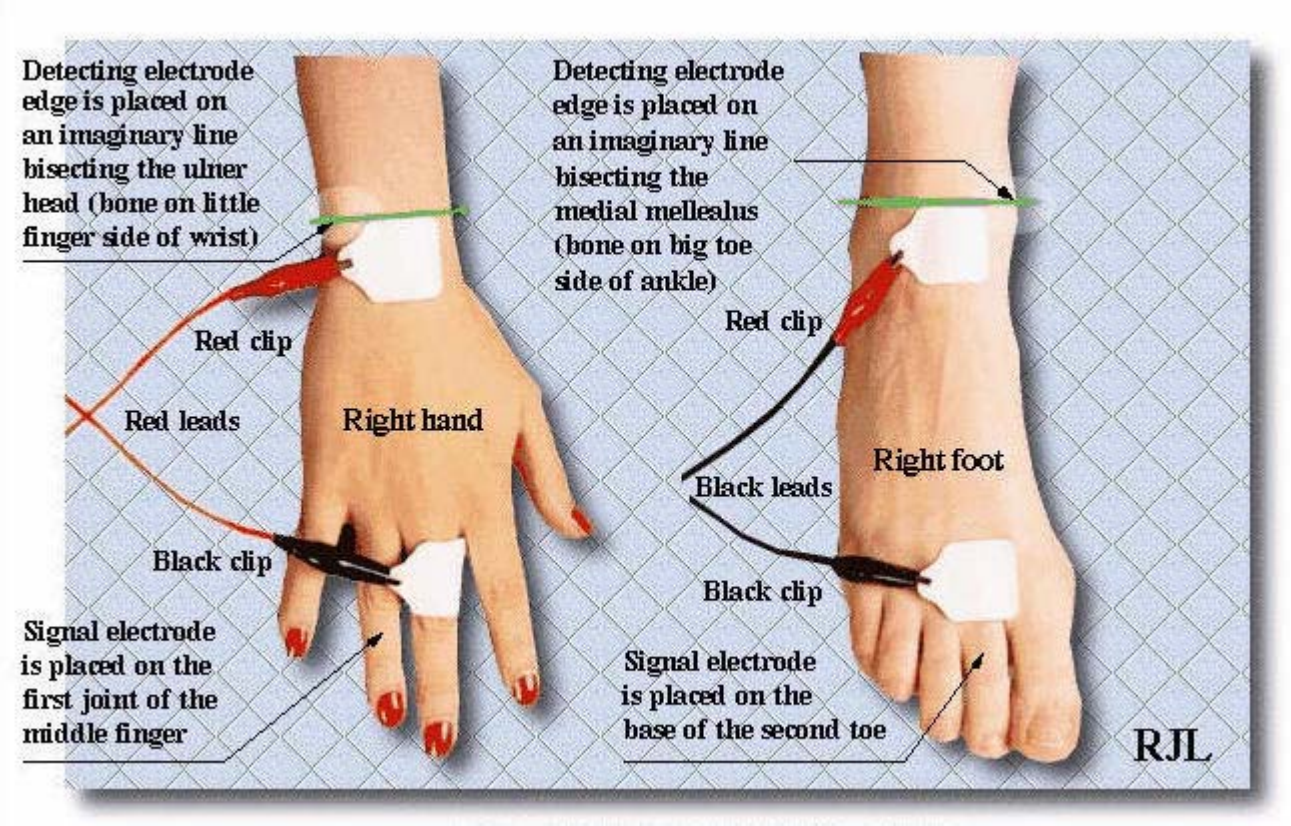
9.D. Bioelectrical Impedance Analysis (BIA) Procedure

9.D.1. Participant Preparation

- The participant should not have exercised or taken a sauna within 8 hours of the study.
- The participant should refrain from alcohol intake for 12 hours prior to the study.
- The participant 's height and weight should be accurately measured and recorded.
- The participant should lie quietly during the entire test.
- The participant should not be wet from sweat or urine.
- The participant should not have a fever or be in shock.
- The study and testing procedure should be explained to the participant.
- The exam area should be comfortable and free of drafts and portable electric heaters.
- The exam table surface must be non-conductive and large enough for the subject to lie supine with the arms 30 degrees from the body and legs not in contact with each other**. If using a hospital bed, the bed should be unplugged prior to testing.**
- The BIA – Quantum II analyzer battery should have a new 9 volt battery.
- The BIA Quantum II analyzer and Spectrum battery should be fully charged.
- The analyzer calibration and patient cables should be checked regularly.
- Record results on the case report form Physical Assessment - [PHYASSESS].

How Electrodes are Placed on the Hand and Foot

BIA TESTING PROCEDURE



9.D.2. Testing Procedure

- The participant should remove the right shoe and sock (generally the study is completed on the right side of the body). The same body side (left or right) should always be used subsequently.
- The participant should lie supine with the arms 30 degrees from the body and legs not touching (take care that upper thighs are not touching) **Remove jewelry on the electrode side** and from around the neck.
- The electrode sites may be cleaned with alcohol, particularly if the skin is dry or covered with lotion. If electrodes do not stick despite use of alcohol, use **NU prep as directed.**
- Attach the electrodes and patient cables as shown in the illustration.
- Turn the analyzer on and make sure the participant refrains from moving. When the measurements have stabilized, record the displayed Resistance (R) and Reactance (Xc) with the participant's name, age, gender, height and weight.
- Remove and dispose of the electrodes. Be careful not injure the participant's skin or contaminate the operator.
- The entire testing time is less than 5 minutes - the BIA analyzer is on for less than one minute.

9.D.3. Operator Proficiency:

- Two consecutive measurements made on a single, stable participant must result in values within one percent.
- Note, the resistance does not lock onto a number because of muscle contractions in the heart. The reading should be the most representative number. If the number varies widely, check electrode placement, jewelry, make sure the bed is unplugged and that the upper thigh is not touching.

9.E. Blood Pressure Management

9.E.1. Overview of Blood Pressure Measurement

In this section, step-by-step procedures for blood pressure measurement in the CRIC Study are presented. It should be emphasized that the steps outlined here can be followed satisfactorily for the vast majority of adult subjects participating in ambulatory follow-up. Exceptional situations occasionally arise with serious obstacles to successful blood pressure measurement. It will be the responsibility of the Training Supervisors in the Clinical Centers to encourage observers to note exceptional circumstances and to seek consultation with the Blood Pressure Consultant when they arise, so that participants will be appropriately evaluated.

You will record results of the blood pressure measurement on the case report form Blood Pressure [BP] Form. Blood pressure is measured at the Screening Visit, Baseline Visit, and every annual clinic visit.

9.E.1.(a). 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.

CRIC participants must abstain from caffeine, smoking, and exercise at least one-half hour prior to and until completion of the blood pressure measurement. Current drug intake, including medications affecting blood pressure and non-prescription drugs, is recorded on the day of the examination.

Try to keep the blood pressure measurement as pleasant as possible. Participants should be given 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 will be standardized, and should take place in a separate, quiet room where no other activity is taking place, and where temperature fluctuations are minimal. Scheduling procedures should try to establish consistent appointment times to minimize as much as possible the impact of daily blood pressure variation. Equipment (including study forms, sphygmomanometer, etc.) should be checked and waiting for the participant.

Allow five minutes of rest in this quiet room after arm measurement and calculation of corrected peak inflation level, but before pulse is measured, which occurs prior to taking the blood pressure. Explain to the participant 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 participant should be relaxed, seated with

back supported with legs uncrossed and feet comfortably flat on the floor, not dangling. The participant should be instructed to refrain from using a cell phone.

The Tycos Classic Hand Aneroid sphygmomanometer will be the standard equipment for all blood pressure measurements at CRIC clinical visits.

In the CRIC Study, sitting and standing blood pressure is measured at the screening, baseline and annual visit in a resting state, using three sitting measurements and one standing measurement.

Correct measurement of blood pressure is important to this study because the study will examine the long-term course of kidney function and risk factors for kidney disease progression. Precision is essential for valid blood pressure measurements. It is essential that the procedures described below for measuring blood pressure are followed exactly.

1. Arm Measurement and Cuff Sizes
    - The proper cuff size must be used to avoid under- or over-estimating the correct blood pressure. To determine the proper cuff size, the observer must measure the arm circumference at the midpoint of the arm at each visit.
    - This measurement is taken on the right arm which has been bared from the shoulder.
    - With the participant standing, holding the forearm horizontal, the arm length is measured from the acromion (or boney extremity of the shoulder girdle) to the olecranon (or tip of the elbow) with a plastic coated metric tape. The midpoint is marked on the dorsal surface.
    - The participant should then relax the arm along the side of the body. The arm circumference is measured by drawing the tape snugly around the arm at the level of the midpoint marking. **Care must be taken to keep the tape horizontal. Also, the tape should not indent the skin.**
    - The chart of arm circumference measurements and corresponding cuff sizes (shown below) is consulted, and the indicated cuff size is checked on the study form and used. (Note: If an arm measures 32.9, 33.0 will be entered. Try to use the same size cuff for every measure within a participant.)
    - Do not use the cuff itself as a measurement device because the ranges marked on the cuff may not correspond with the table. This chart should be consulted for each arm measurement. The markings found on most blood pressure cuffs should **not** be used for reference because they may be incorrect.
2. Determination of Cuff Size Based on Arm Circumference:

Arm Circumference	Cuff Size (cm)
<24.0 cm	**Child, Pediatric, Small Adult**
24.0 to < 33.0 cm	**Adult, Regular**
33.0 to 41.0 cm	**Large Adult**
>41.0 cm	**Thigh, Extra Large**

3. Application of the Blood Pressure Cuff
    - Place the appropriate cuff (as determined in the arm measurement procedure) 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 around the arm, with the palm of the participant's hand turned upward.
    - The wrapped cuff should be secured firmly by applying pressure to the locking fabric fastener over the area where it is applied to the cuff.
4. Stethoscope

A standard Littman stethoscope (or other comparable stethoscope) with a bell should be used. 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.

- The ear pieces should be directed forwards into the external ear canal.
- The ear pieces should be tight enough to exclude outside sound but not so tight that they cause discomfort.
- The valve between the bell and the diaphragm should be turned in the direction of the bell.
- 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.

9.E.2. Blood Pressure Measurement Step By Step

9.E.2.(a). Pulse Measurement

Part of the blood pressure measurement procedure is the measurement of the pulse, as observed by palpation of the radial artery at the wrist.

- The right arm is to be used consistently for measurement of both pulse and blood pressure. If this is not possible, use the left arm. Indicate which arm is used to measure pulse and blood pressure on the case report form.

- 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.
- A good stopwatch should be used for the 5 minute waiting period prior to pulse measurement, 30 second pulse measurement, and 30 second intervals between blood pressure readings.
- The measurement of pulse is performed only after the participant has been seated quietly, with feet flat on the floor, in an erect but comfortable posture, for at least five minutes.
- The patient should refrain from caffeine, smoking, and exercise at least one half hour prior to and until completion of blood pressure measurement.
- The elbow and forearm should rest comfortably on the table. With the palm of the hand turned upward, the radial pulse is palpated and counted for 30 seconds exactly.
- The number of beats in 30 seconds is recorded, multiplied by 2, and the product recorded as the heart rate.

NOTE: Any marked irregularity observed during this period should be called to the attention of the Principal Investigator.

9.E.2.(b). 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 pressure; otherwise, the first of the Korotkoff sounds will be missed. This starting pressure is called the Peak Inflation Pressure and is determined as follows.

- Attach the cuff tubing to the Tycos Classic Hand Aneroid sphygmomanometer.
- While palpating the radial pulse, observe the 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 this value on the BP form.
- When this has been detected, the cuff is quickly and completely deflated.
- The Observed Pulse Obliteration Pressure is then added to 30 mrnHg. This summed value is the Peak Inflation Level. The cuff should be inflated to this level for all readings at this examination. Record this value on the BP form.

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.

9.E.2.(c). Blood Pressure Measurement Procedures

- The seated arm blood pressure is measured three times at each clinic visit. It takes approximately 10 to 15 minutes to make three blood pressure measurements including the initial five-minute rest.

- Blood pressure equipment should be checked prior to seeing the participant. 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 CRIC Study personnel on CRIC participants must be recorded in the database, regardless of the clinical condition of the participant at the time of the measurement.
- All blood pressure measurements taken by CRIC Study personnel should be done using the Tycos Classic Hand Aneroid sphygmomanometer.
- Blood pressure measurements conducted by CRIC Study personnel on CRIC participants should be conducted at the CRIC Study clinic or a satellite office if at all possible. This applies to all study visits.

9.E.2.(d). 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.

9.E.2.(e). Measuring Blood Pressure with a Tycos Classic Hand Aneroid Device

Next, the observer should proceed to carry out the first blood pressure reading. Detailed instructions are given below for measuring blood pressure with a Tycos Classic Hand Aneroid sphygmomanometer.

- Wait at least 30 seconds after complete deflation of the cuff following any preceding inflation.
- Connect the cuff to the Tycos Classic Hand Aneroid device.
- Place the ear pieces of the stethoscope into the ears, with the tips turned forward.
- Apply the bell of the stethoscope over the brachial artery, just below but not touching the cuff or tubing. The brachial artery is usually found at the crease of the arm, slightly toward the body.
- 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.
- 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).

- Open the valve to deflate fully and disconnect the tubing. Remove the stethoscope earpieces from the ears.
- Record the systolic and diastolic reading.
- 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 Blood Pressure Values.
- Note: After the first and second readings, the participant'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.

9.E.2.(f). Standing Pulse and Blood Pressure Measurement

- Ask the participant to stand in a relaxed position with their arms at their sides for two minutes.
- After two minutes, take the pulse measurement in the same location as you did prior to the seated blood pressure measurements.
- Use a bedside table at about waist height for the participant to relax his or her arm upon.
- With the palm of the hand turned upward, the radial pulse is palpated and counted for thirty seconds exactly.
- The number of beats in 30 seconds is multiplied by 2 and recorded on the form.
- Take one standing blood pressure measurement as described above and record the information on the BP case report form.

9.E.3. Forgotten Blood Pressure Readings

If for any reason the observer is unable or has forgotten to complete any portion of the 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. Do not repeat a reading that looks unusual to you.

9.E.4. Reporting the Blood Pressure Results to the Participant

The participant may wish to know his or her results before the form is entered into the database. If so, average the second and third 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.

9.F. Directions for Completing Physical Measures Case Report Forms

Nail Specimen [NSPEC]

Purpose: Record acquisition of nail specimens.

Who: Research Coordinator.

When: Completed at Baseline Visit (Visit #3),
12-month follow-up (Visit #5),
24-month follow-up (Visit #7),
36-month follow-up (Visit #9),
48-month follow-up (Visit #11),
60-month follow-up (Visit #13).

Directions: Refer to Nail Clipping Procedure in Appendix A.

Complete Question #1 of this form even if nail specimens were **not** acquired.

Fingernail clippings are preferred over toenail clippings.

NSPEC will be entered and verified in the Data Management System (***DMS***).

Physical Assessment [PHYASSESS]

Purpose: Record anthropometric measures, Ankle Brachial Index (ABI), and Bioelectric Impedance Assessment (BIA).

Who: Research Coordinator.

When: Anthropometry and Ankle Brachial Index:

Completed at Baseline Visit (Visit #3),
12-month follow-up (Visit #5),
24-month follow-up (Visit #7),
36-month follow-up (Visit #9),
48-month follow-up (Visit #11),
60-month follow-up (Visit #13).

Bioelectric Impedance
Completed at Baseline Visit (Visit #3),
24-month follow-up (Visit #7),
48-month follow-up (Visit #11).

Directions: Refer to the Physical Measures ection in Appendix A for anthropometric measurements, ABI and Bioelectric Impedance Assessment (BIA)directions.

Q.1 - Q.5: Record height, weight, waist circumference.

Q.6 – Q.11: Measure blood pressure on the 3 locations of right side of the body. Repeat these measures on the left side of the body. Record systolic blood pressure only.

Q.12 – Q. 13: Calculate Right AB Index by selecting the higher systolic value between Right Posterior Tibial Artery (PTA) and Right Dorsalis Pedis Artery (DPA) and divide it by the **Right or Left** Brachial Pressure, whichever of these 2 values is higher. Repeat this calculation for the left side. See example in Appendix A.

Complete the BIA section of the form as indicated.

PHYASSESS data will be entered and verified in the Data Management System

Blood Pressure Form [BP]

Purpose: Measure seated blood pressure and pulse.

Who: Research Coordinator.

When: Completed at Screening Visit (Visit #2),
Baseline Visit (Visit #3)
12-month follow-up (Visit #5),
24-month follow-up (Visit #7),
36-month follow-up (Visit #9),
48-month follow-up (Visit #11), and
60-month follow-up (Visit #13).

Directions: Instructions in the Manual Appendix A describe the procedure to measure participant's blood pressure. Standing and seated blood pressure and pulse are noted in the items on the CRF. Brief instructions are also included on the CRF for blood pressure measurement.

Q.1: Date noted is the date of CRIC Study Visit.

Q.2: Time is recorded on a 24 hour clock.

Q.3: Each site will label their equipment sequentially and the label on the equipment will be used for this item.

Q.5: Use a tape measure for mid-point circumference.

Q.6: Recorded this information from the cuff.

Q.7: Measure pulse for 30 seconds and multiply by 2. Record this calculation on the form.

Q.13: Measure pulse for 30 seconds and multiply by 2. Record this calculation on the form.

Note: Elevated values may generate an immediate alert that should be noted on ALERT_I.

Participants with elevated blood pressure may be on anti-hypertensive medications that will be noted on Concomitant Medication (CMED) CRF.

BP data will be entered and verified in the Data Management System (***DMS***).

10. Appendix B: LAB Manual of Procedures

10.A. General Information

This manual has been prepared for the CRIC Study by the Central Biochemistry Laboratory at the University of Pennsylvania under the direction of Daniel J. Rader, M.D. The CRIC Central Lab will provide instruction for specimen acquisition, shipping, tracking, testing, storage and quality control activities associated with the CRIC Study.

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10.B. Case Report Forms Required

Screening Laboratory Results .....[SCRLAB]
Specimen Collection .....[SPECIMEN]
Specimen Transfer – Cold Pack .....[TRANSCOLD]
Specimen Transfer – Dry Ice .....[TRANSDRY]

10.C. Screening Visit (VISIT 2)

10.C.1. Spot Urine Collection Procedure

Encourage participants to stay hydrated even while fasting for the visit. However, do not collect samples after acute fluid load (>24 ounces) or after participant exertion. Collection will be random and, therefore, considered a "spot" urine collection. Participants who have difficulty producing a urine specimen may be offered a glass of water, and subsequent urine specimens may be collected later in the visit to bring the volume up to the required amount.

Spot Urine Collection Instructions:

Both Female and Male participants should void into a separate collection container and then pour the specimen into the urine cup.

- Wash hands before and after voiding.
- Open or remove clothing to make voiding and collection easier.
- Remove the cap from the collection container and have at hand.
- Obtain spot urine collection.
- Use one urinalysis dipstick per patient.
- Dip the strip into the specimen to the indicated line, following the directions on the container label.
- Remove the strip from the specimen
- Read the results by comparing the strip to the label on the dipstick container.
- Be sure to read the strip within the allotted time. Follow the time frame indicated on the dipstick container label.
- Record the results on the screening visit form.

Complete the Screening Lab Results [SCRLAB] Case Report Form [CRF] with the results of the spot urine test for glucose, protein and hematuria.

10.C.2. Screening Visit Blood Collection Procedure

1. Collect one 10mL SST (red/gray top) tube.
    - Allow to clot for 30 minutes
    - Centrifuge for 20 minutes at 2400rpm at room temperature
    - Label two 12x75 polypropylene tubes
    - Transfer serum into two equal aliquots.
    - Send one aliquot to local lab for serum creatinine and glucose testing.
    - Store the second aliquot at -20ºC or -80ºC.
    - If the participant is determined to be eligible and is scheduled for a baseline visit, **send the frozen aliquot to the Central Lab** with the other baseline visit samples according to the pre-arranged monthly schedule.

- Complete the Screening Lab Results [SCRLAB] Case Report Form [CRF] with the results of the serum creatinine and glucose values when you have received the laboratory report by transcribing the values from the report onto the CRF. Also, indicate the result of the urine pregnancy test if this has been performed. Check the entire form for completeness of data.

2. Instructions for 24 hour urine collection.
   - Provide the participant with a urine collection container and leak proof storage container for the 24 hour urine collection in the event that the participant is designated as eligible and will return for the baseline visit.
   - Use permanent marker to label each participant's 3000mL collection container with the ID # and initials.
   - Provide the participant with 24 Hour Urine Collection Instruction sheet.
   - Ideally, the 24 hour urine sample should be collected by the participant the day before the next clinic visit. If this is not possible, the 24 hour specimen cycle may occur up to one week prior to the next clinic visit. In this case, instruct the participant to store the entire specimen in the refrigerator and to keep it as sterile as possible.

10.D. Baseline Visit (VISIT 3)

The Specimen Collection [SPECIMEN] CRF is used to record blood and urine specimen information.

10.D.1. Collection, Processing, and Shipping of 24 Hr Urine Samples

Equipment and Supplies
3000mL urine specimen containers

Urine graduated collection beaker, for men

Kendall Commode Specimen Collection System, for women

Transfer pipettes

15mL graduated urine aliquot tubes

Blank white adhesive labels (Avery #5627)

Urine Collection Labeling
Use permanent marker to label each participant's 3000mL collection container with the patient's initials.

Urine Aliquot Labeling
For the aliquot tubes, use the labels provided with the kit or print labels on the computer indicating that these are 24 hour urine specimens. Three labels will be needed for each participant. For each set of aliquots, handwrite the

collection date and participant's ID number using permanent pen/marker. The labels on the aliquot tubes should be written as follows: NN - NN - NNNN.

1. Preparation of Participants for Urine Collection

In the event that the participant is eligible for the study, urine collection containers and leak proof storage containers for the 24 hour urine collection were provided to the participant at the Screening Visit. Written instructions were also provided

IMPORTANT NOTE: A 24 hour urine sample is considered inadequate if the total volume is less than 500 mls, the total collection time is less than 23 hours or if the result of the total urine creatinine test is less than 7 mg/Kg of body weight. If during completion of the Specimen Colleciton [SPECIMEN] CRF you note that the total volume collected or time of collection is inadequate, do not process the urine aliquots. Discuss with the participant the next appropriate time to collect this sample, review the instructions and provide additional supplies.

2. Urine Aliquot and Storage Instructions

The preparation of a properly mixed aliquot from the 24-hour urine collection is key to the correct measurement of the analyte. Therefore the following procedure must be followed closely:

- 24 hour urine may be measured by thoroughly mixing and pouring the sample into a 2 Liter graduated cylinder. A clean graduated cylinder must be used for each specimen.
- Be sure to record the volume on the requisition and aliquot container.
- DO NOT OVERFILL the aliquot vials. No more than 10mL should be transferred into each aliquot tube.
- Affix pre-printed labels to 3 airtight 15mL graduated conical tubes.
- Transfer urine into aliquots of 10mL each.
- Store 2 of the aliquots at -20^{0}C or -80^{0}C in a plastic rack or cardboard freezer box in an upright position.
- Store the third aliquot at 4^{0}C in a plastic rack or cardboard freezer box in an upright position.
- Label the racks or cardboard boxes with permanent marker or an adhesive label that says "CRIC 24 Hr Urine Refrigerated" or "CRIC 24 Hr Urine Frozen," respectively.

3. Packaging Instructions for Specimens at 4^{0}C

- If the refrigerated samples are in plastic racks, place absorbent material in plastic Ziploc bags and place the samples in Ziploc bags, sealing tightly.
- If the refrigerated samples are in cardboard boxes, rubber band the boxes securely closed.
- Place absorbent material in plastic Ziploc bags and place the boxes in the Ziploc bags.

- Prepare the cold gel packs and place some in the bottom of the mailing container.
- Place the securely wrapped specimens in the mailing container.
- Be sure to put the gel packs securely around the specimens to keep them from shifting or breaking during shipment.
- Replace the styrofoam lid of the mailing container and be sure to include a copy of the Specimen Transfer – Cold Pack [TRANSCOLD] CRF to be shipped to the Central Lab.
- Close the flaps of the outer cardboard sleeve and use packaging tape to securely seal the mailing container.
- Attach the proper mailing labels to the outside of the box.
- Complete the proper shipping form.

4. Packaging Instructions for Specimens at -20^{0}C or -80^{0}C
   - If the frozen samples are in plastic racks, place absorbent material in plastic Ziploc bags and place the samples in Ziploc bags, sealing tightly.
   - If the frozen samples are in cardboard boxes, rubber band the boxes securely closed.
   - Place absorbent material in plastic Ziploc bags and place the boxes in the Ziploc bags.
   - Place a small amount of dry ice in the bottom of the mailing container.
   - Place the securely wrapped specimens in the mailing container.
   - Be sure to pack dry ice securely around the specimens to keep them from shifting or breaking during shipment.
   - Replace the styrofoam lid of the mailing container and be sure to include a copy of the Specimen Transfer – Dry Ice [TRANSDRY] CRF to be shipped to the Central Lab.
   - Close the flaps of the outer cardboard sleeve and use packaging tape to seal the mailing container, but do not seal every seam so that the gas from the dry ice evaporation can escape.
   - Attach the proper mailing labels and dry ice labels to the outside of the box.
   - Complete the proper shipping form.
5. Labeling Instructions
   - Aliquots: label each aliquot with the ID# and visit date.
   - Tubes: label each tube with the ID#, visit date, initials and date of birth.
6. Shipping Instructions
   - Tubes stored at 4^{0}C
     - Ship samples, within 72 hours of creating aliquots, to the Central Lab with cold packs.

- Notify Central Lab of shipment by faxing the Specimen Transfer – Cold Pack [TRANSCOLD] CRF to the Central Lab at *Fax:*215/573-8606.

- Tubes stored at -20^{0}C or -80^{0}C
  - Ship samples once per month, according to the pre-arranged schedule with the Central Lab, to the Central Lab on dry ice.
  - Notify Central Lab of shipment by faxing the Specimen Transfer – Dry Ice [TRANSDRY] CRF to the Central Lab at *Fax:*215/573-8606.

10.E. Collection, Processing, and Shipping of Blood Samples

10.E.1. Equipment and Supplies

1. Blood collection tray
   - A test tube rack to hold the blood collection tubes which are drawn from each participant. These tubes are described in detail in the next section.
   - Three sterile, disposable 21 gauge butterfly needles
   - A plastic vacutainer tube guide
   - Three vacutainer Leur slip adaptors to connect the butterfly
   - Sterile alcohol swabs
   - Gauze sponges
   - A tourniquet
   - Bandages (Band Aids)
   - A stopwatch
2. Blood collection tubes (In the order they are to be drawn)
   - One 10mL Serum red top tube (wrapped in aluminum foil) (BD# 366441)
   - Three 10mL SST tiger top tubes (BD# 366510)
   - Two 5mL Na Citrate (0.105M) blue top tubes (BD# 366415)
   - Two 5mL EDTA purple top tubes (BD# 366452)
   - Seven 10mL EDTA purple top tubes (BD# 366457)

   To facilitate accurate tracking of collected specimens, pre-label each tube with the participant's 8 digit ID number. Use permanent marker or adhesive labels only. The tubes should be in the rack according to the order in which they are to be drawn. Always pre-label the set of collection tubes and aliquot vials prior to the participant's visit, and cross-check the labels with each participant's ID number prior to the phlebotomy.
3. Sample aliquot tray

- A rack to hold the aliquot vials, in the same order as the blood collection tubes are drawn.
- Transfer pipettes
- Absorbent pads to minimize splashing when opening blood collection tubes

4. Sample aliquot vials (In the same order as the blood collection tubes)
   - Two cryogenic vials and two micro packaging vials (light sensitive) for the Serum red top tube
   - Four cryogenic vials for the two 5mL NaCitrate plasma blue top tubes
   - Three 12x75 polypropylene tubes and ribbed plug caps for the three 10mL SST, tiger top tubes.
   - Eight cryogenic vials for two of the 10mL EDTA plasma purple top tubes

   To facilitate accurate tracking of sample aliquots, pre-label each vial with a label indicating that the aliquot is Serum, Light Sensitive serum, EDTA plasma, or NaCitrate plasma, respectively. The vials should also be labeled with the participant's 8 digit ID number. The vials should be set up in the same order as the collection tubes are drawn.
5. Preparation for Blood Collection
   - Preparation for specimen collection is done in the following manner in the early morning, prior to arrival of any participants.
   - Check to make sure the blood collection tray is properly equipped. Every item on the checklist must be ready before proceeding.
   - Check that each vacutainer tube is properly labeled with the appropriate participant number.
   - Check that the sample processing tray is properly equipped. Every item on the checklist must be ready and in its proper position.
   - Check that the aliquot processing tray is properly equipped. Every item on the checklist must be ready and in its proper position.
   - Check that each collection tube and aliquot tube is labeled with the appropriate participant identification number.
   - Check that the centrifuge is working properly. If there is a temperature option, be sure that the temperature is 4ºC ± 2ºC.
   - Check the refrigerator temperature (4ºC ± 2ºC).
   - Check the freezer temperature (either -20ºC ± 10ºC, or -80ºC ± 10ºC).
6. Phlebotomy Room
   - The blood draw should take place in an isolated room or participants should be separated by room dividers.
   - The room is equipped with all of the necessary Blood specimen supplies.

- A separate counter or worktable is equipped with all of the materials and vials that are used in the blood handling and processing.
- The centrifuge, refrigerator, and freezer should be nearby.

7. Precautions for Handling Blood Specimens
   - All specimens are handled as potentially infectious for laboratory workers. Transmissions of the infectious agents associated with Hepatitis and HIV via "needle stick" skin punctures have been documented.
   - Where feasible, wear disposable plastic gloves when collecting and processing specimens. Alternatively, wash hands thoroughly with disinfectant soap prior to leaving the work area. Skin cuts or abrasions should be covered.
   - Use 0.1% sodium hypochlorite (household bleach) to clean up any spills of blood, plasma, or serum. Use this solution to clean up all laboratory work surfaces at the completion of work activities.
   - Dispose of all needles and tubing in puncture-resistant sharps containers for safe disposal.
   - Do not perform any pipetting by mouth.
   - Avoid formation of potentially infectious aerosols by careful pipetting and centrifugation.
   - All used vacutainer tubes, needles, and blood products are to be placed in spill proof liquid biohazard sharps containers for disposal.
8. At participant arrival:
   - Check that the ID number on each tube matches the participant ID.
   - Check that the aliquot tubes are prepared and labeled.
9. Participant Preparation
   - Informed consent must be obtained by the coordinator before drawing blood. This procedure is followed to ensure that the subjects understand the purpose of blood drawing and the possible complications of venipuncture. A standard informed consent has been prepared for this study. With regard to laboratory procedures, the consent statement informs study subjects that there is a small risk of bruising at the spot on the area where the blood is taken. The consent statement also informs study subjects that a copy of the test results is sent to their physician, and that they will be contacted if clinically important tests are abnormal.
   - The subject is asked whether he/she has a bleeding disorder before the blood is drawn. If such a disorder is present, ask the subject whether he/she has had blood drawn previously and if so, whether he/she had any problems with excessive bleeding or bruising at the venipuncture site. If the participant has a history of venipuncture problems, the participant should be sampled only if approved by the physician.
   - Ask the patient if they or their doctor have a preference as to which vein to use to determine whether or not they have been told to protect a particular vein.

- If not, it is recommended that the medial-most antecubital vein in the non-dominant arm is used, assuming that the non-dominant arm will be the access arm of choice, and that the medial most antecubital vein is not likely to be the draining cephalic vein.
- Blood drawing is to be standardized to the sitting position. It is difficult to standardize the length of time that a subject is in the sitting position prior to venipuncture, but to the extent that it is feasible, this should be attempted.

  The venipuncture is performed with a 21 gauge butterfly needle with 12 inches of plastic tubing between the venipuncture site and the blood collection tubes. The butterfly has a small, walled needle which minimizes trauma to the skin and vein. The use of 12 inches of tubing allows tubes to be changed without any movement of the needle in the vein. If the participant is concerned about the venipuncture, he/she may be reassured to know such care is taken. The participant should be given enough time to feel comfortable both before and after the blood collection. In many cases the most memorable part of the experience will be the contact with the technologist who draws the blood and their general attitude and competence.

If the participant is nervous or excited, the technologist briefly describes the procedure, e.g.,

"I am going to be drawing about nine (9) tablespoons of blood. This blood will be used in tests for kidney function, cholesterol and other research analyses. We hope to be able to use the results of these tests to predict who might have a greater risk of kidney and heart disease."

10. Handling participants who are extremely apprehensive about having blood drawn.
    - Do not under any circumstances force the participant to have blood drawn.
    - Explain to the participant that the blood drawing is designed to be as nearly painless as possible. It is sometimes best to let the participant go on with another part of the visit.
    - Have the participant relax in the blood drawing chair just so the phlebotomist can check the veins in the participant's arms, without actually drawing blood.
    - If the participant has "good veins" the phlebotomist can reassuringly say, "Oh, you have good veins; there should be no problem."
11. Venipuncture Procedure Preparation
    - Remove all extra clothing and have the participant sit upright with the sleeves rolled up to expose the antecubital fossa (elbow).
    - A tourniquet is used to increase venous filling. It makes the veins more prominent and easier to enter.
    - PRECAUTIONS WHEN USING A TOURNIQUET:
      - The tourniquet should be on the arm for the shortest time possible.
      - Never leave the tourniquet on for longer than two (2) minutes. To do so may result in hemoconcentration or a variation of blood test values.

- If a tourniquet must be applied for the preliminary vein selection, it should be released and reapplied after a wait of two minutes.
- If the patient has a skin problem, put the tourniquet over the participant's shirt or use a piece of gauze or paper tissue so as not to pinch the skin.

- Wrap the tourniquet around the arm 3 to 4 inches (7.5 to 10.0 cm) above the venipuncture site.
- Tuck the end of the tourniquet under the last round. If a Velcro tourniquet is used, adhere the ends to each other.

12. Identify the vein:
    - Palpate and trace the path of veins several times with the index finger. Thrombosed veins lack resilience, feel cord-like, and roll easily.
    - If superficial veins are not readily apparent, have the participant close his fist.
    - Lowering the extremity over the arm of the chair will allow the veins to fill to capacity.
    - Identify the best available vein.
13. Cleanse the venipuncture site.
    - Remove alcohol pad from its sterile package.
    - Cleanse the vein site with the alcohol pad using a circular motion from the center to the periphery.
    - Allow the area to dry to prevent possible hemolysis of the specimen and a burning sensation to the patient when the venipuncture is performed.
14. Assemble the butterfly-vacutainer set.
    - Attach the Leur adaptor to the vacutainer holder.
    - Attach the Leur end of the butterfly needle set to the Leur adaptor.
15. Perform venipuncture.
    - Grasp the participant's arm firmly, using your thumb to draw the skin taut. This anchors the vein. The thumb should be 1 or 2 inches (2.3 or 5.0 cm) below the venipuncture site.
    - With the needle bevel upward, enter the vein in a smooth continuous motion.
    - Make sure the participant's arm is in a flat or downward position while maintaining the tube below the site when the needle is in the vein. It may be helpful to have the participant make a fist with the opposite hand and place it under the elbow for support.
    - Grasp the flange of the needle holder and push the tube forward until the butt end of the needle punctures the stopper, exposing the full lumen of the needle.
    - Start a timer to measure the flow rate of blood into the first blood collection tube. If the flow rate in the tube is so slow that blood does not fill the first collection tube

within 50 seconds, stop the blood collection and repeat on the other arm. If blood is flowing freely, the butterfly tubing can be anchored to the participant's arm using medical tape for the duration of the draw.

- Remove the tourniquet after blood is flowing into the second tube.
- Keep a constant, slight forward pressure (in the direction of the needle) on the end of the tube. This prevents release of the shutoff valve and stopping of blood flow. Do not vary pressure nor reintroduce pressure after completion of the draw.
- Fill each vacutainer tube as completely as possible; i.e., until the vacuum is exhausted and blood flow ceases. If a vacutainer tube fills only partially, remove the vacutainer and attach another one without removing needle from vein.
- When the blood flow ceases, remove the tube from the holder. The shutoff valve re-covers the point, stopping blood flow until the next tube is inserted.
- **EDTA tubes and NaCitrate tubes should be gently mixed by inverting immediately after each tube is filled and removed from the butterfly setup.**
- If it is not possible to collect all 16 tubes, follow the requested order and fill each tube as completely as possible.

16. Blood Mixing During Venipuncture

- Only invert tubes containing anticoagulant such as EDTA (purple top) and NaCitrate (blue top) collection tubes.
  - To invert tubes, hold the tube horizontal to the floor.
  - Slowly tip the butt end down while watching the air bubble rise to the stopper (1st inversion).
  - When the bubble reaches the stopper, the tube should be at approximately a 22 degree angle to the floor.
  - Next lower the stopper while watching the bubble float to the butt end. Again the tube should be at a 22 degree angle to the floor (2nd inversion).
  - Lower the butt end again. This is the third inversion.
  - Invert each tube eight times. Eight inversions should take 13-15 seconds.
  - DO NOT SHAKE TUBES!!

17. If a blood sample is not forthcoming, the following manipulations may be helpful.

- If there is a sucking sound, the tube has lost its vacuum. Replace with a new tube.
- If no blood appears, move the needle slightly in hope of entering vein. Do Not Probe. If not successful, release tourniquet and remove needle. A second attempt can be made on the other arm.
- The same technician should not attempt a venipuncture more than twice.
- To remove the needle, lightly place clean gauze over venipuncture site. Remove the needle quickly and immediately apply pressure to the site with a gauze pad.

- Discard needle with its cap into a sharps container.

18. Bandaging the arm -
    - Under normal conditions,
        - Slip the gauze pad down over the site, continuing mild pressure.
        - Apply an adhesive or gauze bandage over the venipuncture site after making sure blood flow has stopped.
    - If the patient continues to bleed,
        - Apply pressure to the site with a gauze pad. Keep the arm elevated until the bleeding stops.
        - Wrap the gauze bandage tightly around the arm over the pad.
        - Tell the patient to leave the bandage on for at least 15 minutes.
19. Precautions – If A Participant Feels Faint Or Looks Faint Following The Blood Draw.
    - Have the person remain in the chair, if necessary have him/her sit with head between knees.
    - Take an ampule of smelling salts, crush it, and wave it under person's nose for a few seconds.
    - Provide the person with a basin if he/she feels nauseous.
    - Have the person stay reclined until their color returns and he/she feels better.
    - Place a cold wet cloth on the back of the person's neck.
    - If the person faints, use smelling salts to revive.
    - If the person continues to feel sick, take a blood pressure and pulse reading. Contact a medical staff member, who will advise you on further action.

10.F. Aliquot Processing Instructions

Equipment and Supplies
Centrifuge
Transfer pipettes
Aliquot rack
12x75 polypropylene tubes with ribbed plug or screw caps (leak proof)
2mL cryogenic vials
Light sensitive 2mL cryogenic vials
Balance tubes for centrifuging
Waste disposal containers and sharps container
Cardboard freezer and transport boxes
Ziploc plastic storage bags (for refrigerated samples)
Refrigerator at 4ºC
Freezer at -20 or -80ºC

If the blood flow was not sufficient to collect all 16 tubes of blood, create aliquots in the order described in the Procedure below as completely as possible.

Safety: Obtain and utilize necessary protective clothing/equipment for preparing an aliquot of specimens. Such items include but are not limited to lab coats, gloves, protective eyewear, and absorbent pads.

10.F.1. Centrifuge Instructions

1. Separate and sort any specimens that are not centrifuged (i.e. urine samples, samples to be sent directly to local labs or Central Lab).
2. Loading the centrifuge: Balancing the centrifuge ensures proper performance of the instrument. See Figure 1. Proper Arrangement of Samples in Centrifuge Buckets.
3. Determine the amount of sample volume in each tube and find another tube filled to approximately the same level to ensure correct balancing.
4. Use a "balance tube" filled with water to the proper level if there are an uneven number of specimens
5. After pairing the tubes by their sample volume place them into the centrifuge using the following guidelines:
   - If the centrifuge contains buckets, position the tubes in the buckets so that the tube and its match are located in opposite buckets (mirror image of each other). Select holes in the opposing buckets that allow for equal weight distribution. See Figure 1.
   - In most small centrifuges there are wells for tube positioning. Place the tube pairs into the wells so that the tubes are exactly opposite in position.
   - Once the centrifuge is loaded with samples, set the speed for 2400rpm, temperature for 10ºC, and time for 20 minutes. Start the centrifuge.
   - Once the centrifuge is stopped, open the centrifuge and remove the specimens.
   - Locate and arrange the specimens by participant to keep each set of specimens and aliquots organized.
   - Identify and perform any special handling (protect from light, freeze, etc) to those specimens that require it.
6. Preparation of an aliquot sample:
   - Aliquot samples are necessary any time the original specimen collection tube or container cannot be used in performing the requested tests, transporting the specimen, or storing the specimen.
   - Verify that the specimens have been properly centrifuged and cells have been clearly separated.
   - Use a disposable transfer pipette to transfer the sample from the primary tube to the appropriately labelled secondary tubes, in this case 12x75 polypropylene tubes and cryogenic vials.

- When removing plasma or serum using a transfer pipette be very careful not to disturb the white cell layer or the serum separator layer.

7. Procedure (See Table 1)
   - One 10mL Serum (red top) tube, wrapped in aluminum foil:
     - Allow to clot for 30 minutes
     - Centrifuge for 20 minutes
     - Affix labels to 4 aliquot cryovials; 2 normal cryovials, 2 light sensitive cryovials
     - Transfer serum from tube into 4 equal aliquots in 2 normal cryovials and 2 light sensitive cryovials.
     - Store aliquots at -20ºC or -80ºC on site.
   - Three 10mL SST (red/gray top) tubes:
     - Allow to clot for 30 minutes
     - Centrifuge for 20 minutes
     - Affix labels to 3 12 x 75 polypropylene tubes
     - Transfer serum to make one aliquot per collection tube
     - Refrigerate samples at 4ºC to be sent to Central Lab
   - Two 5mL NaCitrate (blue top) tubes:
     - Within 1 hour, centrifuge for 20 minutes
     - Affix labels to 4 aliquot cryovials
     - Transfer plasma from first tube into 2 equal aliquots, from second tube into 2 equal aliquots.
     - Store at -20ºC or -80ºC on site.
   - Two 5mL EDTA (purple top) tubes:
     - Affix label to one tube for HbA1C and refrigerate at 4ºC to be sent to Central Lab.

       NOTE: HbA1C [Tube #7 in Table 1] is drawn only on participants identified as diabetic on the CRF after the baseline visit.
     - Affix label to second tube and send to local lab for CBC.
   - Seven 10mL EDTA (purple top) tubes:
     - Within 1 hour, centrifuge two tubes for 20 minutes
     - Affix labels to 8 aliquot cryovials
     - Separate plasma into 8 equal aliquots
     - Store at -20ºC or -80ºC on site

- Affix labels to the other 5 tubes and refrigerate at 4ºC to be sent to Central Lab

- Label the racks or cardboard boxes with permanent marker or an adhesive label that says "CRIC Blood Refrigerated" or "CRIC Blood Frozen," with dates, patient numbers, etc.
- Ship blood and urine samples by Federal Express to the Central Lab Monday through Thursday **ONLY**. Monthly shipped samples must be shipped on a pre-arranged schedule, which will allow the Central Lab to stagger the arrival of samples for ease of processing.

10.F.2. Packaging Instructions for Specimens at 4^0C

1. If the refrigerated samples are in plastic racks, place absorbent material in plastic Ziploc bags and place the samples in Ziploc bags, sealing tightly.
2. If the refrigerated samples are in cardboard boxes, rubber band the boxes securely closed.
3. Place absorbent material in plastic Ziploc bags and place the boxes in the Ziploc bags.
4. Prepare the cold gel packs and place some in the bottom of the mailing container.
5. Place the securely wrapped specimens in the mailing container.
6. Be sure to put the gel packs securely around the specimens to keep them from shifting or breaking during shipment.
7. Replace the styrofoam lid of the mailing container and be sure to include a copy of the Specimen Transfer – Dry Ice [TRANSDRY] CRF to be shipped to the Central Lab.
8. Close the flaps of the outer cardboard sleeve and use packaging tape to securely seal the mailing container.
9. Attach the proper mailing labels to the outside of the box.
10. Complete the proper shipping form.

10.F.3. Packaging Instructions for Specimens at -20^0C or -80^0C

1. If the frozen samples are in plastic racks, place absorbent material in plastic Ziploc bags and place the samples in Ziploc bags, sealing tightly.
2. If the frozen samples are in cardboard boxes, rubber band the boxes securely closed.
3. Place absorbent material in plastic Ziploc bags and place the boxes in the Ziploc bags.
4. Place a small amount of dry ice in the bottom of the mailing container.
5. Place the securely wrapped specimens in the mailing container.
6. Be sure to pack dry ice securely around the specimens to keep them from shifting or breaking during shipment.
7. Replace the styrofoam lid of the mailing container and be sure to include a copy of the Specimen Transfer – Dry Ice [TRANSDRY] CRF to be shipped to the Central Lab.

8. Close the flaps of the outer cardboard sleeve and use packaging tape to seal the mailing container, but do not seal every seam so that the gas from the dry ice evaporation can escape.
9. Attach the proper mailing labels and dry ice labels to the outside of the box.

10.F.4. Labeling Instructions

1. Aliquots: label each aliquot with the ID# and visit date.
2. Tubes: label each tube with the ID#, visit date, initials and date of birth.

10.F.5. Shipping Instructions

1. Tubes stored at 4^0C
   - Ship samples, within 72 hours of creating aliquots, to the Central Lab with cold packs.
   - Notify Central Lab of shipment by faxing the Specimen Transfer – Cold Pack [TRANSCOLD] CRF to the Central Lab at
     Fax: 215/573-8606.
2. Tubes stored at -20^0C or -80^0C
   - Ship samples once per month, according to the arranged schedule, to the Central Lab on dry ice.
   - Notify Central Lab of shipment by faxing the Specimen Transfer – Dry Ice [TRANSDRY] CRF to the Central Lab at
     Fax: 215/573-8606.

10.G. Collection, Processing, and Shipping of Nail Samples

Equipment and Supplies

100 % Stainless steel clippers with attached collection device
Sample storage vials with hinged snap cap
Blank white adhesive labels

Supplies:

Neat Clipper available at: VSO & A Marketing
169 Marion Street
Winnipeg, Manitoba, Canada
R2H OT3
Phone: 1-204-982-7211 Fax: 1-204-982-7219

Specimen storage container for the nail clippings:
Fisher brand sample vial with Hinged snap cap.
Opaque – 1.5oz (45mL)

Case of 600 available through the
Fisher Scientific Catalog - #03-341-75C

10.G.1. Nail Sample Labeling

- Use the labels provided with the kit or print labels on the computer to indicate that these are CRIC Nail samples.
- Handwrite the participant's collection date, and 8-digit ID number and initials.
- Label the specimen vial prior to the collection of the nail samples.

10.G.2. Collection Procedure

- See Appendix A of this manual for the nail collection procedure.
- Store the specimen vials in a container labeled "CRIC Nail Samples."
- Store nail samples on site at room temperature. They may be shipped to the Central Lab once per month.

10.G.3. Packaging Instructions

- Place 2 or 3 sample vials in each plastic Ziploc bag, sealing tightly.
- There is no need for absorbent material in the Ziploc bags.
- Place the securely wrapped specimens in the mailing container.
- There is no need for Styrofoam mailing containers as the specimens are kept at room temperature.
- Be sure to put packing material securely around the specimen containers to keep them from shifting or breaking during shipment.
- Be sure to include the paperwork to be shipped to the Central Lab.
- Close the flaps of the outer cardboard sleeve and use packaging tape to securely seal the mailing container.
- Attach the proper mailing labels to the outside of the box.
- Complete the proper shipping form.
- Ship blood and urine samples by Federal Express to the Central Lab Monday through Thursday **ONLY**. Monthly shipped samples must be shipped on a pre-arranged schedule, which will allow the Central Lab to stagger the arrival of samples for ease of processing.

Figure 1. Proper Arrangement of Samples in Centrifuge Buckets

The letters correspond to patient sample tubes

A	**B**	**C**	**D**
E	**F**	**G**	**H**
I	**J**	**K**	**L**

L	**K**	**J**	**I**
H	**G**	**F**	**E**
D	**C**	**B**	**A**

Opposite Centrifuge Buckets (Arranging 4 samples)

A			
		C	

	C		
			A

Table . Sample Processing Flow Sheet

Tube		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Tube 1	10mL Serum (red top)	Allow to clot for 30 minutes	Centrifuge for 20 minutes at 2400 rpm	Affix labels to 4 aliquot cryovials; 2 normal, 2 light sensitive	Transfer serum into 4 equal aliquots	Store aliquots at -20ºC or -80ºC	Ship to Central Lab once per month
Tube 2	10mL SST (tiger top)	Allow to clot for 30 minutes	Centrifuge for 20 minutes at 2400 rpm	Affix label to one12x75 polypropylene tube	Transfer serum into one aliquot	Refrigerate sample at 4ºC	Ship to Central Lab within 72 hours
Tube 3	10mL SST (tiger top)	Allow to clot for 30 minutes	Centrifuge for 20 minutes at 2400 rpm	Affix label to one12x75 polypropylene tube	Transfer serum into one aliquot	Refrigerate sample at 4ºC	Ship to Central Lab within 72 hours
Tube 4	10mL SST (tiger top)	Allow to clot for 30 minutes	Centrifuge for 20 minutes at 2400 rpm	Affix label to one12x75 polypropylene tube	Transfer serum into one aliquot	Refrigerate sample at 4ºC	Ship to Central Lab within 72 hours
Tube 5	5mL NaCitrate (blue top)	Within 1 (one) hour	Centrifuge for 20 minutes at 2400 rpm	Affix labels to 2 aliquot cryovials	Transfer plasma into 2 equal aliquots	Store aliquots at -20ºC or -80ºC	Ship to Central Lab once per month
Tube 6	5mL NaCitrate (blue top)	Within 1 (one) hour	Centrifuge for 20 minutes at 2400 rpm	Affix labels to 2 aliquot cryovials	Transfer plasma into 2 equal aliquots	Store aliquots at -20ºC or -80ºC	Ship to Central Lab once per month
Tube 7	5mL EDTA (purple top)	Affix label for HbA1C**	Refrigerate at 4ºC	Ship to Central Lab within 72 hours	** After the baseline visit, drawn only on participants identified as diabetic.		
Tube 8	5mL EDTA (purple top)	Affix label for CBC	Refrigerate at 4ºC	Send to local lab for CBC			
Tube 9	10mL EDTA (purple top)	Within 1 (one) hour	Centrifuge for 20 minutes at 2400 rpm	Affix labels to 4 aliquot cryovials	Transfer plasma into 4 equal aliquots	Store aliquots at -20ºC or -80ºC	Ship to Central Lab once per month
Tube 10	10mL EDTA (purple top)	Within 1 (one) hour	Centrifuge for 20 minutes at 2400 rpm	Affix labels to 4 aliquot cryovials	Transfer plasma into 4 equal aliquots	Store aliquots at -20ºC or -80ºC	Ship to Central Lab once per month
Tube 11	10mL EDTA (purple top)	Affix label to collection tube	Refrigerate sample at 4ºC	Ship to Central Lab within 72 hours			
Tube 12	10mL EDTA (purple top)	Affix label to collection tube	Refrigerate sample at 4ºC	Ship to Central Lab within 72 hours			
Tube 13	10mL EDTA (purple top)	Affix label to collection tube	Refrigerate sample at 4ºC	Ship to Central Lab within 72 hours			
Tube 14	10mL EDTA (purple top)	Affix label to collection tube	Refrigerate sample at 4ºC	Ship to Central Lab within 72 hours			
Tube 15	10mL EDTA (purple top)	Affix label to collection tube	Refrigerate sample at 4ºC	Ship to Central Lab within 72 hours			

10.H. CRIC Durable Equipment List

Freezer: Fisher Under-counter Freezer (-20 C), Cat. # 97-926-1, $1121.05
Refrigerator: Marvel Scientific Refrigerator (+1 to + 7 C), Cat. # 13-985-16, $1245.00
Centrifuge: Clay Adams Compact II Centrifuge, Cat # 22-289446, $565.62

Disposable Equipment List

Blood Collection Tubes:

10mL SST red/gray top tubes	BD# 366510, Fisher Cat# 02-657-11
10mL Serum red top tubes	BD# 366441, Fisher Cat# 02-683-60
5mL Na Citrate blue top tubes	BD# 366415, Fisher Cat# 02-685-6B
5mL EDTA purple top tubes	BD# 366452, Fisher Cat# 02-685-2C
10mL EDTA purple top tubes	BD# 366457, Fisher Cat# 02-683-84

Blood Aliquot Tubes:

Fisherbrand 12x75 polypropylene tubes	Fisher Cat # 14-959-16A
Ribbed plug caps	Fisher Cat# 14-959-20
Nalgene cryogenic vials Mfr # 5000-1020	Fisher Cat# 03-337-7Y
Nalgene micro packaging vial (light sensitive)	Nalgene Mfr # 362805-0020

Urine Collection Containers:

Fisherbrand 3000mL specimen storage containers	Fisher Cat# 02-540-32
Kendall Commode Specimen Collection System, for women	Fisher Cat# 14-375-180
Fisherbrand 10 oz graduated collection beaker, for men	Fisher Cat# 02-544-201

Urine Aliquot Tubes:

Falcon Blue Max Jr. 15mL graduated tubes	Fisher Cat# 14-959-49B

Nail Clipping Collection

Fisherbrand sample vial with hinged snap cap. Opaque. 1.5oz (45mL)
Case of 600 Fisher Cat# 03-341-75C

Shipping List

Fiberboard freezer boxes:

2” high for small aliquot tubes	Fisher Cat#11-678-24A
with 9 x 9 inserts	Fisher Cat# 11-678-26D
Rubber bands for freezer boxes	
Fisherbrand specimen bags for refrigerator boxes	Fisher Cat# 01-800-06
Absorbent material (paper towels, pads) in plastic bags	Fisherbrand Cat# 06-670-35
Refrigerant gel packs	Fisher Cat# 03-528B
Styrofoam mailers with outer cardboard sleeves:	
Small (8x6x4) 4C samples	Fisher Cat# 11-676-14
Medium (11x11x12 ¼) for -20 or -70C samples	Fisher Cat #03-530-17

Dry ice labels
Dry ice (2.2kg or 5lb per mailing container) – See local University Vendor
Packaging tape
Mailing labels (provided by carrier)

10.I. Completing Laboratory Specimen Case Report Forms

Screening Laboratory Results [SCRLAB]

Purpose: Record results of local laboratory tests to determine participant eligibility at screening visit.

Who: Research Coordinator.

When: Completed at Screening Visit (*Visit #2*).

Directions: Local laboratory results are recorded on this CRF. Study eligibility is determined by the serum creatinine value measured at this visit.

Q.3: Use the following Institution Laboratory Code to identify the testing lab:

CC ID	LAB CODE	Laboratory Name	Location
01	100	University of Pennsylvania	Philadelphia, PA
01	101	Pepper Laboratory, U of PA	Philadelphia, PA
02	200	The John Hopkins University	Baltimore, MD
02	201	John Hopkins Medical Laboratories - Pathology	Baltimore, MD
02	202	ProHealth - Quest Laboratories	Baltimore, MD
02	203	University of Maryland - University of Maryland Medical System	Baltimore, MD
03	300	Case Western Reserve University	Cleveland, OH
03	301	Central GFR Laboratory at the Cleveland Clinic Foundation	Cleveland, OH
03	302	University Hospitals of Cleveland	Cleveland, OH
03	303	The Cleveland Clinic Foundation	Cleveland, OH
03	304	MetroHealth Medical Center	Cleveland, OH
04	400	University of Michigan at Ann Arbor	Ann Arbor, MI
04	401	University of Michigan Medical Center	Ann Arbor, MI
04	402	St. Clair Specialty Physicians	Detroit, MI
04	403	Detroit Medical Center University Laboratories	Detroit, MI
05	500	University of Illinois at Chicago	Chicago, IL
05	501	UIC Clinical Pathology Laboratories	Chicago, IL
06	600	Tulane University Health Science Center	New Orleans, LA
06	601	Medical Center of Louisiana at New Orleans (MCLNO)	New Orleans, LA
07	700	Kaiser Permanente of Northern California	Oakland, CA
07	701	University of California, San Francisco	San Francisco, CA
07	702	Summit Medical Center Laboratory	CA

Q.5: This specimen will be sent to the Central Laboratory, University of Pennsylvania, if the participant is enrolled in the Cohort. If the participant does not qualify or is not enrolled in the Cohort, the specimen is discarded.

Q.6-7: Site-based laboratory results are recorded for creatinine and glucose. Record values as they are written on the laboratory report source document.

Q.9a-c: Follow directions from the dipstick manuacturer to determine if the result is positive or negative.

Q.10: "Not Done" will be checked for males or post-menopausal females. Source documentation must be available to confirm female participant's post-menopausal status

SCRLAB data will be entered and verified in the Data Management System (***DMS***).

Specimen Collection [SPECIMEN]

Purpose: Record blood/serum and urine specimen status at collection and shipment.

Who: Research Coordinator.

When: Completed at Baseline Visit (Visit #3),
12-month follow-up (Visit #5),
24-month follow-up (Visit #7),
36-month follow-up (Visit #9),
48-month follow-up (Visit #11), and
60-month follow-up (Visit #13).

Directions: Refer to Laboratory Procedure Manual in Appendix B.

Information on this CRF will assist the Central Laboratory personnel in noting the date and time of the collection and the condition of the blood and urine specimens. This data will help determine whether the specimens shipped are utilizable for laboratory analysis.

This CRF is considered a "Single" CRF and can be entered multiple times per visit in the data management system. This may occur when the specimen is not utilizable and rejected by the Central Laboratory and is re-collected. The CRF can be completed again at the site with a new date.

Q.2: Date of birth will assist the Central Laboratory personnel determine normal ranges, if age is applicable.

Q.2a: Gender response is checked as either "Male" or "Female". This allows the system to generate gender-based normal values to assess significance of the results.

Q.3: A diagnosis of diabetes mellitus, given by a healthcare professional, will prompt the RC to collect and the laboratory personnel to expect Specimen #7 – 5 ml purple top tube –for HbA1C analysis.

NOTE: Specimen #7 is collected for all participants at baseline. However, at annual follow-up visits, this specimen is collected on diabetic participants only.

Q.8: If the Central Laboratory personnel determine that the 24-hour urine is not adequate for analysis, they may request another 24-hour urine sample. The value for total creatinine in urine should not be less than 7 mg/kg of total body weight.

Q.9 Spec. #: The grid identifies the tubes of blood and the 24-hour urine specimen by a numbering system, which subsequently helps identify the possible aliquots from each tube on Specimen Transfer (TRANSDRY and TRANSCOLD) CRFs. Nail specimen and Serum Creatinine Specimen have also been assigned numbers for tracking purposes in the DMS.

Spec. #7: Purple top - 5 ml tube is collected at Baseline Visit for all participants and for diabetic participants **only** during follow-up visits. At follow-up visits, check "No" for specimen collection, and "Not required" as reason for participants who are not diabetic.

This CRF is completed by the Research Coordinator and a ***copy*** is included in the shipping container for Central Laboratory Personnel use.

Data on the SPECIMEN CRF will be entered and verified in the DMS, by the Research Coordinator at the site.

Specimen Transfer – Cold Pack [TRANSCOLD]

Purpose: Record specimen status during the shipping process.

Who: Research Coordinator and Central Laboratory personnel.

When: Frozen specimens are shipped to the Central Laboratory within 72 hours of collection and processing.

Directions: Refer to Laboratory Procedure Manual in Appendix B.

Processed and stored specimens listed on this CRF will be shipped to the Central Laboratory at the University of Pennsylvania no later than 72 hours after collection.

Q.1: The grid lists the specimens that are expected to be shipped to the Central Laboratory within 72 hours of collection.

Spec. #: These numbers correlate with the numbers and the corresponding tube on the SPECIMEN CRF.

Seq. #: This column is shaded, indicating its use by the SDCC for internal tracking purposes.

The RC will record the status of the shipped specimens. Central Laboratory personnel will assess the condition of the received specimens by checking the information in the appropriate columns. Specimens not shipped will not require a response.

Spec. #7: This specimen will be collected on diabetic participants only at follow-up visits. The RC will check "Specimen Not Available" at shipping, for non-diabetic participants.

The RC will complete the contact information and alert the Central Laboratory by faxing the completed CRF on the day of shipping.

When the shipment is received and the condition recorded, Central Laboratory personnel will fax the completed CRF to the RC.

The RC will enter and verify TRANSCOLD information in the DMS **after** the completed CRF is faxed from the central laboratory.

Specimen Transfer – Dry Ice [TRANSDRY]

Purpose: Record specimen status during the shipping process.

Who: Research Coordinator and Central Laboratory personnel.

When: Frozen specimens are shipped to the Central Laboratory once a month.

Directions: Refer to Laboratory Procedure Manual in Appendix B.

Processed and stored specimens listed on this CRF will be shipped to the Central Laboratory at the University of Pennsylvania once a month, on a schedule described by the Central Laboratory in the laboratory manual.

Q.1: The RC will record the date and time when specimens were processed and frozen.

Q.2: The grid lists the specimens that are expected to be shipped to the Central Laboratory once a month on dry ice.

Spec. #: These numbers correlate with the numbers and the corresponding tube on the SPECIMEN CRF.

Seq. #: This column is shaded, indicating its use by the SDCC for internal tracking purposes.

The RC will record the status of the shipped specimens. Central Laboratory personnel will assess the condition of the received specimens by checking the information in the appropriate columns. Specimens not shipped will not require a response.

The RC will also complete contact information on the CRF and alert the Central Laboratory by faxing the completed CRF on the day of shipping.

When the shipment is received and the condition recorded, Central Laboratory personnel will fax the completed CRF to the RC.

The RC will enter and verify the information on TRANSDRY in the DMS **after** the completed CRF is faxed from the central laboratory.

10.J. Lab Transfer Schedule

10.J.1. Monthly Shipping Schedule for CRIC Centers

First **– Maryland Centers**

- Monday – Johns Hopkins (ProHealth), U. of Maryland

Second **– Pennsylvania and Ohio Centers**

- Monday – Central Lab will pick up from U. of Penn Lab
- Wednesday – Case Western Reserve University (University Hospitals of Cleveland, Cleveland Clinic Foundation, Metro Health Medical Center)

Third **– Michigan and Illinois Centers**

- Monday – U. of Michigan, St. Clair Specialty Physicians
- Wednesday – U. of Illinois at Chicago

Fourth **– Louisiana and California Centers**

- Monday – Tulane U. Health Science Center
- Wednesday – Kaiser Permanente of Northern California and U. of California, San Francisco

24 Hour Urine Collection Participant Instructions

An accurate test begins with proper collection of the urine specimen. Test results may be inaccurate if the specimen is collected at the wrong time, stored improperly, or contaminated. You will always be asked to collect the specimen yourself, so you should follow these instructions to be sure it is done properly. It is best if you do this test the day before your visit. If you can't, you can collect it up to one week before the next visit. Store the entire specimen in the refrigerator

Instructions:

START TIME: 1. *Upon waking, empty your bladder and discard urine.*

_____ ←— ***Write the time here as the START TIME.***

DATE: 2. *Write the **date and the start time** on the label provided with THE REQUEST SLIP.*

_____

FROM THIS POINT FORWARD, ALL URINE FOR THE NEXT 24 HOURS MUST BE COLLECTED.

Use a **separate container at each voiding**
Avoid contamination with feces, etc.
Empty urine into the larger container.
Keep the larger container **refrigerated** during the entire collection period.

FINISH TIME: *3. Upon waking the next day, the **FIRST** urine must be **COLLECTED**.*

_____ ←— ***Write the time here as the FINISH TIME.***

DATE: *4. Write the **date and the finish time** on the label provided with the REQUEST SLIP.*

_____

11. Appendix C: ECG Manual of Procedures

[See separate manual entitled: CRIC Central ECG Reading Center (CERC) for the Chronic Renal Insufficiency Cohort (CRIC) Study.]

Electrocardiograph Transfer [ECGTRANS]

Purpose: Record status at administration and transfer for study-related ECGs.

Who: Research Coordinator.

When: Completed at Baseline Visit (Visit #3),
12-month follow-up (Visit #5)
24-month follow-up (Visit #7)
36-month follow-up (Visit #9)
48-month follow-up (Visit #11) and
60-month follow-up (Visit #13).

Directions: This CRF records pertinent information when administering / performing ECGs at the sites. The completed CRF is faxed to Wake Forest Central Reading Center.

Q5: Cart # represents location to Wake Forest ECG Reading Cnter. This is entered for the purpose of ultimately corresponding with the reading center as to ECG reports. It is a numerical combination of clinical center and site number.

EXAMPLE: U of Penn will record 101 in this field. Tulane will record 601.

Q6: Gender: The RC must record “Male” or “Female” based on birth gender.

Q9: Wake Forest Central Reading Center will confirm the receipt of ECG to the site and the RC will note that on the CRF. If the Central Reading Center does not confirm the receipt of the ECG, the RC will call to verify.

ECGTRANS data will be entered and verified in the Data Management System (DMS).

12. Appendix D: GFR Manual of Procedures

12.A. Introduction – Glomerular Filtration Rate (GFR)

Based upon our experiences with both (1) routine clinical GFR testing, and (2) clinical study protocols utilizing GFR testing, we find that a thorough introductory explanation of the GFR testing procedure should be given to every patient at their initial GFR testing visit. This introduction serves as the main opportunity for patient education and as a tool with which the technologist can meet their testing aims:

1. PATIENT EDUCATION
   - calming effect on patient; decreased anxiety
   - helps patient do what is requested; overview of test steps; anticipates patient questions
   - introduces the technologist; patient/technologist interaction is important; test success is proportional to contact time
   - conveys importance of test to patient; importance of test to overall study
2. PRESENT THE APPROPRIATE MESSAGE
   - Test explanations should be tailored to each patient's ability to understand the material and to their individual needs.
3. TECHNOLOGIST TESTING AIMS
   - assess patient status; mental/physical; any special problems
   - establish authority; knowledge of theory and practice of test; ask "Do you have any questions?"
   - establish contact; be friendly professional; proper dress; allay fears; emphasis on doing the test together; respect privacy during test collections

12.B. Patient Hydration

1. CRIC Hydration Procedure
   - Water is used exclusively
     - Exception: pre-test light meal (< 10 grams protein) is permitted
   - Defined hydration levels:
     - prior to arrival for test: one quart (1000 ml) drunk the evening prior to the gfr test; 5 ml/kg (350 ml/12 oz for a 70-kg patient) drunk the morning of the gfr test before arrival

- between SSKI administration and first urine collection following the iothalamate injection (Uo) : 10 ml/kg (700 ml/24 oz for a 70-kg patient)
- for the remainder of the test following the first (Uo)urine collection: 200 to 400 ml/hour (equivalent to flow rate of 3.3-6.7 ml/min at equilibrium)

- Hydration goals:
  - establish a desirable urine flow rate of >3 ml/min: and, as an absolute minimum, a flow rate of >1 ml/min
  - limit the variability of urine flow rate between individual urine collections as much as possible

2. Hydration Tips
   - The defined hydration levels (1.b above)are meant as a guide and may be altered, for any specific test, at the discretion of the GFR technologist.
   - Tap water is adequate for hydration if it has no disagreeable taste, odor, color, etc., and is acceptable to the patient. Distilled water should be used if indicated. The water temperature should be cool but not cold; large volumes of cold water can chill the patient and adversely affect the test (delayed gastric emptying and bloating, possible nausea, vasoconstriction, voiding difficulty).
   - For patients with relatively better GFR (approx >50 ml/min), water drunk will take at least 30 minutes to alter urine flow. For patients with lower function, this hydration lag might be one to two hours. Therefore, for patients with significantly decreased GFR (approximately < 40 ml/min), liquid intake should be increased the evening prior to the GFR test visit and hydration the morning of the test before arrival at the clinic) is critical. Even for relatively higher-functioning patients, this hydration may prevent voiding problems caused by high dietary sodium intake and/or minimal hydration in the everyday diet.

12.C. Thyroid "Blockage" With Super-Saturated Potassium Iodide

1. Principle

   The thyroid gland usually has some unused (empty) storage capacity for iodine, which it uses to synthesize the metabolic hormones thyroxine and triiodothyronine, and it routinely absorbs circulating iodide from the blood stream. The 35 microCurie dose of 125I-sodium iothalamate which is administered to the patient for the CRIC gfr study, contains about 140 micrograms of iodine. About 99% of this iodine is bound to the iothalamate molecule, and about 1.0 micrograms of 125-iodine is free for thyroid uptake. Please note that this is less

than 1/40 of the FDA recommended daily dietary allowance (RDA) for iodine. To prevent thyroid uptake of this free radioactive iodine, a pre-test dose of super-saturated potassium iodine (SSKI) or Lugol's Iodine is given to the patient. This "cold" iodine temporarily fills the remaining thyroid iodine storage space and the circulating 125-iodine then cannot be absorbed by the organ and, instead, is cleared by the kidneys.

2. Pharmaceuticals
    - Super-saturated potassium iodide (SSKI, potassium iodide oral solution, USP)
    - Lugol's Iodine (strong iodine, USP)
    - Administered as a five-drop dose, by mouth, in about 20 ml (0.5 oz) of water, at least 30 minutes prior to iothalamate injection
    - Iodine dose per five drops:
      SSKI: approx. 190 mg iodide
      Lugol's: approx. 13 mg iodine + 19 mg iodide
3. Pharmacokinetics
    - One dose (minimum of 30 mg iodide) of either of these pharmaceuticals reduces the thyroid uptake of radioiodide by at least 97% at 24 hours following the isotope dose.
    - Uptake is reduced for several days.
4. Adverse Reactions

    The only significant adverse reaction to these thyroid-blocking agents is an allergic reaction to the iodine. Indeed, an iodine allergy is an exclusion criterion in the CRIC Study. Fortunately, true iodine allergy is very rare; in 30 years of clinical GFR testing on 10K+ patients, the Renal Lab personnel at CCF have only encountered about two dozen cases. Reaction to iodine-containing contrast media is not necessarily the same as an allergy, rather, it may be a systematic reaction to a large (multi-milliliter) bolus dose of contrast. Patients who exhibit true iodine allergy usually know that they are, indeed, allergic and report trips to the emergency room following seafood dinners, etc. We at CCF have performed iothalamate GFR tests on patients who have questionable iodine reactions, after administration of prophylactic doses of Benadryl. In cases where serious, documented iodine allergy exists, iothalamate GFRs should not be performed.

    Theoretically, an allergy to the iothalamate molecule itself could exist, but no such allergy has been reported to our knowledge.

The only other reaction reported is an acute case of "swollen glands" (parotitis) following a dose of SSKI/Lugol's; this causes the patient no discomfort, and the GFR can be done.

12.D. Urine Collection Procedures

1. General Considerations
   - collections:
     - background urine sample (i.e. before isotope injection}; aliquot for gfr
     - five additional timed urine collections for the GFR (a “discard” collection followed by four sequential gfr collections)
   - special patient issues:
     - specific voiding problems are an exclusion criterion
     - non-anatomic voiding problems are usually due to hydration problems or patient nervousness/comfort issues (see PATIENT VOIDING PROBLEMS section below)
2. Collection Completeness/Accuracy Issues
   - Historically, GFR techniques employed bladder catheterization to insure complete collections; our method uses voluntarily voided collections to avoid discomfort and risk of infection.
   - Urine collect1ons are the largest source of error in renal clearance GFR testing; two urine factors in the numerator of the final GFR calculation equation directly affect the result:

     GFR = UV/P

     Where U = concentration of isotope in urine and

     V = urine flow in ml/min
   - Specific maneuvers to help insure collection accuracy:
     - increase urine flow rate (V) by providing significant hydration; decreases both bladder retention and delay in ureters
     - instruction of patient: initial introductory explanation plus repeated visit reminders
     - attention to collection "mechanics"
     - attention to collection timing
     - accurate volume measurement/a1iquoting
     - measures to avoid collection "crossover" counts
     - proper labeling of samples

3. Details Of Patient Instruction For Collections
    - First visit most important (see separate section, INTRODUCTORY EXPLANATION OF THE GFR); beginning of the patient's "learning curve" for GFR testing, i.e. what the patient must do for each urine collection
    - At each visit, "reminders" repeated before each collection reinforce the desired behaviors: (1) take time to empty bladder completely, 2) collect all the urine, (3)indicate the moment you finish, (4) leave the sample in the designated place
    - Patient behaviors we are trying to avoid:
        - attempting to urinate as rapidly as possible in the belief that, because you are noting the collection beginning and ending times, their voiding speed is being timed
        - "holding back" and not emptying the bladder because they are used to providing aliquots, i.e. please fill this (small) bottle, or think they will not be able to provide a sample at the next voiding time
        - not indicating the moment when they finish urinating, as opposed to when they finish washing their hands and open the restroom door two minutes later
        - carrying the urine sample (a biohazard and weakly radioactive sample) out into the hall to hand it over to you (if they don't spill it first)
4. Details Of Collection "Mechanics"
    - Use Universal Precautions
    - Size of containers: large enough so that one or two containers will hold up to approx. 800 ml. Especially for elderly patients, it is preferable to provide one large container so that, once urination has started, the stream will not be interrupted.
    - Male patients: one-liter tri-cornered plastic graduate (beaker), one-liter plastic male urinal, 24-hour plastic jug, 12 oz. cups (if small volumes are passed)
    - Female patients: 800-ml plastic Speci-pan ("hat")
    - Collection tips:
        - patient voids, but appears to retain urine and mentions that they can void again five minutes later; use double-void technique before drawing blood sample
        - female patient loses part of specimen in toilet even when using Speci-pan; next time use two Speci-pans placed "back-to-back" in bowl

- female patient is having period and collections have small amount of blood; do test as usual
- patient has bowel movement at time of collection and specimen contains feces; not usable; must start a, new collection period (see below)
- patient (or tech) spills sample before volume is measured, or loses part of sample in toilet; not usable; must start a new collection period
- urine flow rate for the collection is < 1 ml/min; save the entire collection; do not draw blood; must pool collections (see below)

- Starting a new collection when a sample is unusable
  - note the time of collection of the unusable urine specimen; this will be the start time of the new collection period
  - discard the unusable urine collection
  - draw a blood sample; this is the blood at the start of the new urine collection period
  - proceed as usual, waiting a minimum of 30 minutes before collecting the new urine
- Pooling collections when flow is inadequate
  - Save entire low-volume collection
  - do not draw blood sample
  - acutely increase hydration if indicated, to boost flow
  - wait a meaningful period of time before attempting a new collection, i.e. 30 minutes minimum
  - collect complete new urine specimen
  - pool (mix) new and saved collections
  - if pooled urine volume gives a flow rate > 1 ml/min, draw the usual post-collection blood sample
  - proceed with any remaining GFR periods, as usual

5. Details Of Collection Timing
   - The accuracy of urine collection timing directly affects the accuracy of the GFR results by altering the V factor in the GFR equation: GFR = UV/P
   - The isotope concentration in the urine excreted by the kidneys can change relatively quickly with changing hydration, which also affects the U factor

- For these reasons, we note the clock time at the moment each urine collection is complete; the patient must call out or knock on the restroom door, etc. to signify the collection is finished
- Time is noted to the nearest minute

6. Details Of Volume Measurement/Aliquoting
   - Volume must be measured using the appropriate-sized graduated cylinder, to the nearest estimated milliliter; do NOT round volumes to larger volume increments; do NOT measure volumes with volume scales printed on the sides of Speci-pans, urinals, etc.
   - Aliquoting is best done from the original collection container to avoid "crossover" counts (see below); aliquot directly into the mailing/backup tubes with a syringe and then measure the collection volume in a graduated cylinder, adding the aliquoted volume to the measured number
   - Label aliquots accurately
7. Details To Avoid Collection "Crossover" Counts
   - Definition: "crossover" counts are isotope counts in a urine sample which occur as contamination from a previous urine collection
   - Two measures which eliminate this contamination:
   - proper aliquoting (see section 6 immediately above)
   - thorough rinsing of measuring containers
8. Patient Nervousness/Comfort Issues
   - Patient's mental status can adversely affect urine collections
   - Factors affecting patient comfort:
     - sense of privacy during collection
     - relaxed, unhurried voiding of specimen
     - location of restroom
     - temperature, lighting, comfort of testing area
     - temperature, taste, etc. of hydration water
     - interaction with GFR tech and others
     - other patient factors:
     - are they in a hurry to leave?
     - have they been stuck multiple times?
     - have they become ill during the test (fasting/hydration)?

12.E. GFR Testing Phlebotomy Techniques

1. General Considerations
    - Samples to be drawn:
        - preliminary (i.e. before the isotope injection) blood samples for the GFR, biochemistry, etc.
        - five additional blood samples for the gfr test
    - Special patient issues:
        - anatomic access problems: paralysis, previous lymph: node surgery, scarring, amputation
        - other patient problems: aversion to indwelling lines, arthritis/back problems, etc. affecting patient positioning
        - ultimate issue: Do we have a single vein we must protect at all costs, or do we have the luxury of several sites?
    - Desirable features of phlebotomy
        - free-flowing blood sampling
        - secure location
        - acceptable patient comfort
2. Evaluating The Patient For Phlebotomy: Recommendations
    - Do not follow the advice of the patient without looking at their arms for yourself.
    - Look at both arms before proceeding; note alternative sites in case the first attempt fails; five extra minutes invested before you insert a line may help you avoid twenty minutes of grief when a bad line fails in the middle of the test.
    - Give the patient some item to squeeze (e.g. ball, roll of tape) as they make their fist; the veins will "stand up" better. If the patient's arms are very muscular, it is sometimes better to have them relax, rather than making a fist. Veins in the bend of the elbow are more palpable if the elbow is slightly bent.
    - Tighten the tourniquet sufficiently or use a blood pressure cuff to dilate the veins; tie the tourniquet over the shirtsleeve if the patient complains of pinching
    - If dilated veins are not apparent when the patient's arms are supported on a drawing chair or desktop, use gravity to your advantage by re-positioning the arm on a pillow placed in the patient's lap, so that it angles down toward the floor; blood pooling may make the veins stand out.

- If heat is used to dilate the veins, use hot towels, and not heating pads, which usually not hot enough to achieve the desired effect.
- To maximize your sense of fingertip touch, palpate veins on unbroken skin with an ungloved hand; glove the hands just prior to line insertion. Wear correctly-sized gloves; if gloves are tight, fingertip touch is compromised. If your hands are cold or chapped, making vein location difficult, purposely wear gloves for several minutes until the hands warm up and touch improves.
- Use Universal Precautions; tip: use disposable latex tourniquets and discard/replace them often (i.e. between patients) to avoid biohazard contamination.
- Do not tape down a newly inserted line to excess — it only has to last a few hours, and taping it may occlude the line by forcing the needle/catheter against the vein wall)
- It is preferred that heparin flush be used to keep phlebotomy lines open between draws; use at least 100 units/ml flush. You may use a normal saline flush if it is the Hospital or Nursing Office policy to use saline-only flushes.

3. Phlebotomy Supplies
   - "One-time" blood drawing equipment
     - Vacutainer-type tube holder with needle
     - Syringe with needle
   - Multiple draw lines:
     - butterfly-type needle (i.e. scalp-vein needle or solution set); 21 gauge X 3/4" or 23 gauge X 3/4" with 12” line ending in luer fitting with removable cap;
     - 20 gauge X 1.25" or 22 gauge X 1" flexible plastic catheter + stylet set (i.e. Angiocath or Insyte)
     - heparin-lock usage following initial draw; 100 U/ml
4. Phlebotomy Line Insertion And Blood Draws
   - Use Universal Precautions
   - Chose the largest appropriate vein, preferably in the anticubital area of the non-dominant arm
   - Butterfly usage:
     - after insertion, draw pre-injection samples using vacutainer tube holder with screw-in luer adaptor to draw directly into tubes; can use syringes, but see section 5(B) immediately below
     - remove holder/adaptor unit and use 100 U/ml heparin flush to clear line

- check line for patency at approx. 15 min. intervals
- draw blood samples after urine collections as in section 1. immediately above, but draw a minimum 3 ml discard tube before the desired sample to insure that no heparin flush remains to dilute the sample

- Catheter usage:
  - insert catheter and cap immediately with a six-inch catheter extension set (Baxter Interlink or similar); draw pre-injection blood samples as in section IV.,C, l. immediately above
  - heparinize as in section IV,C,2 above
  - draw subsequent samples as in sections IV,C,3 and IV,C,3&4
- Sample labeling: it is imperative that all samples be labeled immediately as they are drawn
- Line removal
  - As usual; maintain pressure for 5 minutes, then, provide bandage

5. Phlebotomy Tips
   - Usually, draw samples without tourniquet; tourniquet can be used, but if used, never place above the upper arm injection site.
   - Drawing samples directly into tubes with Vacutainer holder/luer adaptor eliminates biohazard (transfer of blood from syringes to tubes) and saves cost of syringes.
   - Blood samples NOT timed; draw as soon as urine collection is measured or safely temporarily stored (approx. 5 min.); blood levels of isotope change only slowly because of subcue route of administration; if draw is delayed, note on GFR form.
   - If line clots off and it will be hard to restart immediately: get the blood sample you need with a "single-draw" method, and then take time to re-establish the line.
   - A particularly convenient technique for securing a catheter in place is to tape it down with a sterile, transparent catheter dressing (e.g. Johnson & Johnson Bioclusive, 2 X 3 in.)

12.F. GFR Test Protocol

The trained GFR technologist will perform the required GFR tests according to the test protocol. Training by the Central GFR Lab from the Cleveland Clinic Foundation will insure a common understanding of the testing technique. If a Clinical Center technician needs advice during a test, he or she should call the GFR Lab for advice on how to proceed. Written explanations of any deviations from the test routine should be included on the GFR worksheet.

Urinary clearance of the GFR marker, Glofil (^{125}I-Iothalamate), after subcutaneous injection will be used to determine accurately the level of glomerular filtration in subjects with renal insufficiency by a method independent of changes in lean body mass or changes in protein intake. The patient ingests an oral water load, is given a saturated solution of potassium iodine (SSKI), and the Glofil is injected subcutaneously. After a 60-90 minute waiting period, timed collections of urine and serum are performed. GFR is equal to the urinary clearance of the marker.

12.F.1. Materials and Equipment

1. To perform GFR
   - Saturated solution of potassium iodide (SSKI)
   - Scale to weigh patient
   - Drinking cup and pitcher of water
   - Accurate timing device (digital clock and/or stop watch)
   - Urine collection containers (paper cups with lids, speci-pans or "hats" for females, urinals for males)
   - Graduated cylinder to measure urines
   - Blood specimen supplies (needles, syringes, tubes, alcohol wipe, gauze, a tourniquet or a blood pressure cuff, 0.9% saline, heparin-1,000 unit/ml, paper tape, band aid, and any other supplies)
   - Dose of Glofil
2. To process samples: (Only use equipment designated for radioactive specimens)
   - Refrigerator to store samples
   - Centrifuge
   - Tubes to store backup duplicate samples at the center
   - Mailing supplies supplied by the Central GFR lab (labels, tubes, zip-lock bags, mailers, ice packs, and packaging tape).
3. GFR PROTOCOL AMENDMENT #1

   Throughout the protocol procedure section where the intravenous (IV) catheter is used to draw a blood sample, it is permissible to substitute the **same amount of normal saline solution for a heparin solution flush** to clear the IV tubing. This blood draw procedure is repeated four times during the course of a GFR test.

12.F.2. GFR Test Procedure

1. Check eligibility prior to initiating the GFR test.

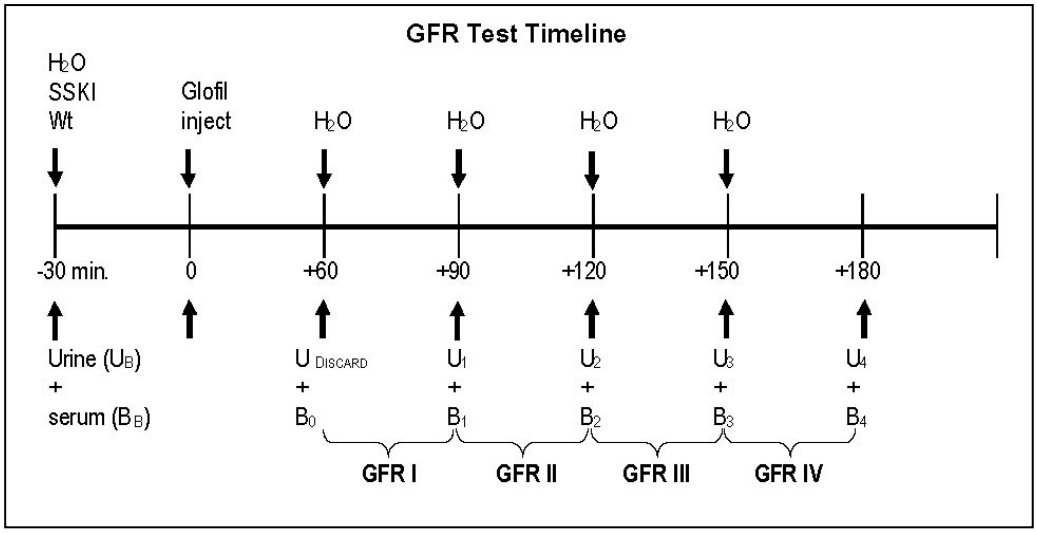
2. Fasting is **NOT** required for this test. Participants may consume a light meal prior to the GFR test; however, the protein content of the meal must be less than 10.0 grams. Participants should avoid caffeinated beverages. A list of recommended meals and foods to choose from will be provided for participants prior to the GFR test. These guidelines refer to the meal immediately preceding the GFR. For example, for patients having the GFR performed in the morning, the breakfast meal should follow these guidelines; for patients having the test in the afternoon, lunch should be limited in protein content as described above. Every effort should be made to perform all GFR procedures on an individual patient under the same conditions each time, that is, at the same time of day.
3. **Non-steroidal anti-inflammatory agents** taken on an as needed basis (i.e., **not** taken daily as a maintenance medication) including aspirin and ibuprofen, should be withheld for at least 48 hours prior to each GFR test. All other drugs that participants may require, including acetaminophen, should be taken up to and including the morning of the GFR test as usual.
4. **Women of childbearing potential (post-pubertal, premenopausal, and not surgically sterilized) must have a urine pregnancy test, within 72 hours prior to the GFR determination. The GFR must be canceled if the pregnancy test was positive or if the patient did not have the test. Written results must be on file whether the pregnancy test is done outside of the Clinical Center or at the Clinical Center. If written results are not on file, a urine pregnancy test must be done on the morning of the GFR.**
5. If the patient has had a radionuclide diagnostic test in the past month, using an isotope other than ^{99}Technetium or ^{125}I, the GFR must be rescheduled. The most common example of such a test is a thallium stress test.
6. Patients should drink one quart of water the evening before the study. In addition the patient should have a 5 ml/kg water load at home the morning of the study.
7. Record the patient's height (cm) and weight (kg).
8. Mix 5 drops of SSKI in 20 ml of water and give to the patient orally. Record the time given. (The SSKI prevents thyroid uptake of any free ^{125}I. This protects the patient and eliminates error in the GFR determination due to the additional elimination route for the isotope).
9. Start hydrating the patient. A water load of 10 ml/kg is required during the next 90 minutes.
10. Draw the background blood sample and the appropriate Biochemistry samples after inserting the heparin lock, but before the Glofil injection. The recommended procedure for drawing GFR samples is as follows:
    - The subject should be seated during venipuncture.
    - It is recommended that the blood be drawn from an arm vein using an I.V. catheter/needle unit with a heparin lock. A recommended set is a 22

ga. 1 in. Insyte-W (Becton-Dickinson vascular access, cat. no. 3884221) and 6" catheter extension set (Baxter Interlink, cat. no. 2N3374 with the injection site removed, and Vacutainer tube holder with a screw-on leurlock adapter (Becton-Dickinson cat. no. 367290). The 6-inch line allows free motion for tube changes.

- Insert the I.V. catheter into the vein. Draw all the biochemistry samples and the GFR baseline sample. Immediately after obtaining the samples, heparinize the site with at least one ml. of 100 u/ml heparin or normal saline solution.
- After heparinization, the line may be re-capped. The needle should be taped down securely with paper tape or some other easily removed hypoallergenic tape. Avoid taping the needle down to an extreme degree; this may pinch off the flow of blood.

11. Collect background urine; record the time.
12. At least 30 minutes following the administration of the SSKI, the Glofil is injected subcutaneously in the upper arm. Record the time.
13. Continue to hydrate the patient at the rate of 200-400 ml/hour as tolerated throughout the study.
14. At least 60 minutes after the time of the Glofil injection, the patient should void. Record the time (time #0). Measure the urine volume. See "Procedure Notes," item 3 of this section. If this volume is at least 250 ml then continue with the test (go to Step #11 immediately below). If it is less than 250 ml, wait a full 90 minutes from the time of the Glofil injection. Have the patient void again. Record the time. Pool both urines to determine the volume of the discard urine. If the combined volume of urine is at least 250 ml, continue with the test. If the volume is still inadequate, try another discard at 120+ minutes. If, after 120+ minutes, the total is at least 250 ml, continue with the test. If not, call the Central GFR Lab for advice.
15. Draw a blood sample (S-#0--7 cc SST red/gray tube) using the heparin lock. To draw GFR samples, use two tubes for each draw. With the first tube, draw 2 ml. of heparin/blood to avoid diluting the GFR sample. Discard this initial diluted sample; then draw the GFR sample in the second tube. Always re-heparinize promptly. The heparinized solution may be used repeatedly for the same patient, but be sure to keep the syringe capped between draws.
16. After a minimum of 30 minutes (or more, depending on the ability of the patient to void), collect the next urine sample (U-#1). Record the time. Measure the volume. (If the flow rate for the period is low, extend the period to get additional urine and a higher flow rate, as described in #10 above). The flow rate for urines U-# 1 through U-#5 is required to be > 1.0 ml/min.
17. Draw the next blood sample (S-#1). Re-heparinize the line.
18. Repeat steps 12 and 13 until four timed urines have been collected and appropriate blood samples drawn.

19. When all the blood samples have been obtained, remove the I.V. catheter. Have the patient apply moderate pressure at the site for five minutes to avoid bleeding; then apply a bandage.



12.F.3. Preparing the Samples for Mailing to the Central GFR Lab

1. When the blood samples have clotted, centrifuge the blood samples.
2. Be sure to include the patient's name code and number on each of the pre-labeled tubes.
3. Place half of the serum in an appropriately labeled tube; a minimum of 1 ml must be sent. Save the rest as a backup sample in the refrigerator. (Discard the duplicate when GFR results are received unless you are asked to submit the backup sample labeled with the QCID for quality control of the Central GFR Lab).
4. Place ***three aliquots of <u>each</u> of the five measured urine specimens*** in the appropriately labeled tubes. A minimum of 1 ml must be sent. For each set of three aliquots:
   - One aliquot is sent to the GFR Central Laboratory.
   - The second is sent to the CRIC Central Biochemistry Lab.
   - The third sample should be saved in the refrigerator. (It can be discarded when GFR results are received.)
5. Tighten all the caps of the mailing tubes.
6. Prepare the mailer for shipping with one frozen ice pack in the bottom of the inner Styrofoam box.
7. Place all GFR tubes ***[5 urine and 6 serum samples]*** in a zip-lock bag. Place a paper towel in the bag to absorb any leakage that might occur. Attach a piece

of yellow/magenta tape with a message "radioactive" on the outside of the bag. These bags should be flattened by hand to remove air and sealed.

8. Place the zip-lock bag containing all the GFR samples into the inner Styrofoam box. Place the Styrofoam lid on the Styrofoam inner box.
9. Slip the Styrofoam inner box into the cardboard outer shipping box. Place the completed GFR data form on top of the Styrofoam box lid. The outer cardboard box should then be sealed with packing tape.
10. GFR samples should be sent by next-day mail service to the GFR Central Laboratory address:

    CRFC Central GFR Lab, Desk A51

    Cleveland Clinic Foundation

    East 102nd Street

    Cleveland, Ohio 44195

11. A subset of samples [5 urine aliquots described in step #4 above] will be sent to the CRIC Central Biochemistry Lab to measure urine creatinine for calculation of UV/P creatinine clearance during the same four time periods to allow direct comparison for creatinine clearance and GFR.

    CRIC Central Biochemistry Lab

    University of Pennsylvania

    421 Curie Boulevard, Room 645 BRBII/III

    Philadelphia, PA 19104-6160

IMPORTANT NOTE: DO NOT SEND SAMPLES TO LABORATORIES ON FRIDAYS/HOLIDAYS TO AVOID STORAGE AND SHIPPING PROBLEMS.

12.G. Radiation Safety Considerations for GFR

1. YOU ARE ALWAYS BEING EXPOSED
   - We are constantly being exposed to natural "background" radiation in our everyday lives; the level of exposure varies with your location. Specifically, your local exposure is related to (1) the local geology, and (2) the local altitude. Local geology includes naturally occurring soil and rock concentrations of radioactive isotopes, including: those in water supplies, food, the air, etc. Local altitude relates directly to the level of radiation exposure due to cosmic rays.
2. EXPOSURE LIMITS FOR “OCCASIONAL” ISOTOPE USERS
   - Set by the U.S. National Committee on Radiation protection (NCRP)
   - Limits for non-occupational workers are generally 1/10 those for everyday users (in the sense of nuclear medicine department employees)

- Limits are for ionizing radiation, i.e. x-rays and isotope-decay by-product radiation, not ultrasound or MRI (magnetic resonance imaging) exposure
- Present limits:
  - whole body dose equiv. = 500 mrem/yr
  - eye lens = 150 mrem/yr
  - extremities = 5000 mrem/yr
  - skin = 5000 mrem/yr
- Regardless of limits, the Nuclear Regulatory Commission expects licensees to promote a standard referred to as the "as low as reasonably achievable" or ALARA principle: exposures will be kept as far below the limits as is reasonably achievable."

3. ^{125}I-SODIUM IOTHALAMATE (GLOFIL)
   - Derivative of iothalamic acid; related to Conray contrast media, but non-radioactive iodine atoms replaced with "hot" 125-iodine
   - M.W. = 643
   - chemical concentration: 1 mg/ml
   - activity: 1 milliCurie/4 ml
   - 60-day nuclear half-life
   - approximately 90-minute biological half-life (normal GFR)
   - FDA approved for renal studies (GFR)
   - weak gamma emitter; average energy 30 kEv
   - iodine dose per 35 microCuries is approx 140 micrograms
   - half-value layer: 0.0037 cm of lead
   - 40 day shelf-life
   - sole U.S. manufacturer/distributor: Questcor Pharmaceuticals, Inc., Union City, CA
4. RADIATION SAFETY HOUSEKEEPING
   - Worker-specific protection
     - follow the three main principles of radiation safety to minimize exposure: maximize distance from the source
     - minimize exposure time
     - utilize shielding
     - clothing -- the clothing standard for Universal precautions is acceptable; liquid impermeable; gloves; face shields for transferring

- shielding

  except for the original manufacturer's dose vial, the only shielding required would be the dose (syringe) holder for the dose in transit; the dose syringe does not need a shield during injection; bio-samples are too dilute to pose a significant hazard

  the half value layer for 125-I is 0.0037 cm of lead

- hygiene

  hand washing

  no eating, smoking, etc. in isotope area

  minimize risk of ingesting isotope

- personnel monitoring

  film badge

  ring

  thyroid counts

- limited exposure time
- mazimize exposure distance

- Work area cleaning, etc.
  - area monitoring

    meter survey: map of work area; meter readings above surfaces; upper limit of acceptable defined by RSO; monthly records

    wipe tests: map of work area; wipe areas lOOcm2; upper limit of acceptable defined by RSO; monthly records

  - surface protection — absorbent paper: Chux, rolled plastic-backed paper
  - shielding — usually none

    cleanup

    limit spill with absorbent paper

    block access to area and prevent traffic as needed

    notify RSO if appropriate

    wash surface with detergent and water

    wipe liquid up; monitor

    repeat until no residual counts above background

    monitor personnel shoes, coats, etc.

- liquid disposal — urine disposal in toilet usually; disposal in approved isotope sinks
- solid trash disposal

  labeled/bagged

  incinerator/decay/landfill

12.H. Completing I-GFR Case Report Forms

Glomerular Filtration Rate [GFR]

Purpose: Assess kidney function by measuring clearance rate of a filtration marker from the plasma by the kidneys for participants assigned to GFR sub-Cohort.

Who: Research Coordinator.

When: Completed at Baseline Visit (Visit #3),
24 month-follow-up (Visit #7) and
48 month-follow-up (Visit #11).

Directions: Enter the data on this form into the electronic DMS as soon as possible. **This form must be entered into the DMS by the time the samples are received at the Lab. This is essential in order for the lab to complete their calculations and report test values.**

Send a photo copy of this form with the samples in the packing crate.

Refer to the GFR Manual in Appendix D for administering GFR test to the participant.

Q.4-5: If the participant has consumed more a meal containing more than 10.0 grams of protein, GFR testing should be rescheduled.

Q.6-7: These questions are for female participants only. N/A response is acceptable only for male participants or female participants who are post-menopausal. Source documentation must be available to confirm female participant's post-menopausal status. Urine pregnancy test date must fall within 72 hours of GFR test date.

A positive pregnancy test will exclude a participant from GFR testing.

Q.8: If the response to this question is ***YES***, the test must be rescheduled for a date at least ***30 days*** from the radionuclide test. The most common example of such a test is a thallium stress test.

Q.9-9a: If NSAIDs or aspirin are taken within 48 hours of GFR test and are not part of a daily prescribed regimen, the test will be rescheduled for 48 hours after last use.

Q.12a-d: If discard urine volume is less than 250 ml, hydration must be continued, with a wait period of another 30 minutes and the new time will be reported in ***12a*** and the new volume reported in ***12b***.

Complete the remainder of the form indicating time, urine volume and blood draw. Space is provided for comments.

GFR data will be entered and verified in the Data Management System (***DMS***) ***within 24 hours***.

GFR – Specimen Transfer [GFRTRANS]

Purpose: Record specimen status at collection and transfer for GFR testing.

Who: Research Coordinator, GFR Central Laboratory personnel and University of Pennsylvania Central Laboratory personnel.

When: Completed at Baseline Visit (Visit #3),
24-month follow-up (Visit #7), and
48-month follow-up (Visit #11).

Directions: Refer to Appendix D GFR testing.

The RC will record the information in Q.1, Q.2, specimen availability for GFR Central Laboratory and University of Pennsylvania Central Laboratory, shipping information and RC contact information.

The GFR Central Laboratory personnel and the University of Pennsylvania Central Laboratory personnel will complete information in relation to the receipt and condition of the specimen.

Q.1-2: Date and time specimen was processed and frozen will be recorded.

Q.3: Specimen status for GFR Central Laboratory lists serum and urine specimens collected at specified intervals during GFR testing. For each serum or urine specimen collection period, availability of the specimen and whether the specimen is shipped is recorded by checking the appropriate box.

Q.4: Specimen status for University of Pennsylvania Central Laboratory lists urine specimens collected at specified intervals during GFR testing. For each urine specimen collection period,

availability of the specimen and whether the specimen is shipped is recorded by checking the appropriate box.

Specimen will be shipped to the GFR Central Laboratory and University of Pennsylvania Central Laboratory. Laboratory personnel at each Central Laboratory will determine whether the specimen is received, and if received, whether the specimen is in an acceptable condition.

Prior to shipping, the RC will advise both Central Laboratory personnel of the shipment of specimens to be received the following day, by faxing the GFRTRANS CRF. This will help the laboratory personnel anticipate the shipment and also notify the RC if the shipment is not received as scheduled. When the shipment is received, and the condition of the specimens determined, the laboratory personnel will fax the completed CRF to the RC.

If specimens are sent on different days, the RC will record information on separate CRFs, indicating a different shipping date for each shipment. A copy of the completed CRF will be sent with the shipment.

When the completed CRF is received at the site, the RC will enter and verify the data in the data management system.

MEALS WITH < 10 GRAMS OF PROTEIN

The breakfast meals below have less than 10 grams of protein. You may recommend one of the combinations, or recommend items from each meal.

Breakfast Meal # 1	**Protein (g)**
½ cup low-sodium hot or cold cereal	2
½ cup low-fat or skim milk*	4
½ medium apple	0.15
½ cup orange juice	0.15
Hot coffee or tea, with 1/4 cup non-dairy creamer	0.50
Total:	**6 .8**

*can substitute 1/2 cup non-dairy creamer (1 g protein) for milk

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Breakfast Meal # 2	
1 plain bagel (3 inch diam.) or English muffin with butter or jelly	4
½ medium banana	0.60
1 cup apple juice	0.30
Hot coffee or tea, with 1/4 cup non-dairy creamer	0.50
Total:	**5.4**

Breakfast Meal # 3	
2 slices bread with butter or jelly	4
½ cup applesauce, sweetened or unsweetened	0.20
½ cup cranberry juice	0
Hot coffee or tea, with 1/4 cup non-dairy creamer	0.50
Total:	**4.7**

Breakfast Meal # 4	
2 frozen 4 ½ inch waffles	4
½ cup strawberries	0.45
½ cup apple juice	0.15
Hot coffee or tea, with 1/4 cup non-dairy creamer	0.5
Total:	**5.1**

Breakfast Meal # 5	
1 cup yogurt	8
1 four-inch rice cake with jam or jelly	1
Hot coffee or tea, with 1/4 cup non-dairy creamer	0.5
Total:	**9.5**

Breakfast Meal # 6	
1 boiled egg	7
1 slice of bread with butter or jelly	2
1 cup cranberry juice	0
Hot coffee or tea, with 1/4 cup non-dairy creamer	0.50
Total:	**9.5**

The lunch meals below have <u>less than 10 grams</u> of protein. You may recommend one of the combinations, or recommend items from each meal.

Lunch Meal #1	**Protein (g)**
Half of a peanut butter and jelly sandwich	6.0
one slice bread	
1 tablespoon peanut butter	
jam or jelly	
1 medium fresh banana	1.2
Cookie	1.34
1 cup apple or orange juice	0.30
Soda, flavored water	0
Total:	**8.84**

Lunch Meal #2	
Baked potato (2-1/3 X 4-3/4 in)	4.65
w/ one pat butter	0.05
½ cup mixed vegetables	2.64
1 medium fresh apple	0.30
1 cup apple or orange juice	0.30
Soda, flavored water	0
Total:	**7.94**

Lunch Meal #3	
1 cup vegetable soup	4.5
Lettuce and Tomato Sandwich with oil, vinegar, or mayo	4.42
2 slices bread	
1 leaf lettuce	
2 slices tomato	
½ cup pre-packaged fruit salad/fruit cocktail	0.51
1 cup apple or orange juice	0.30
Soda, flavored water	0
Total:	**9.73**

Lunch Meal #4	
½ cup pasta, plain (e.g. spaghetti, macaroni)	3.36
½ cup spaghetti sauce	2.24
Salad:	
½ cup lettuce,	
½ cup tomatoes	
2 tablespoon salad dressing (French, Italian)	3.40
1 cup apple or orange juice	0.30
Soda, flavored water	0
Total:	**9.3**

13. Appendix E: Questionnaires

USE OF THE DIET HISTORY QUESTIONNAIRE
IN THE CHRONIC RENAL INSUFFICIENCY COHORT STUDY

Authors: Cheryl Anderson, PhD, MPH and Shiriki Kumanyika, PhD, MPH, RD
CRIC Scientific and Data Coordinating Center, University of Pennsylvania

The Diet History Questionnaire (DHQ) is a food frequency questionnaire (FFQ) developed by staff at the National Institutes of Health-National Cancer Institute's (NIH-NCI) Risk Factor Monitoring and Methods Branch. It will be used in the Chronic Renal Insufficiency Cohort Study (CRIC) to assess dietary factors associated with progression of CRI and cardiovascular disease in renal insufficiency.

13.A. General Concept: What is a Food Frequency Questionnaire?

A FFQ consists of a food list, and a frequency and portion size response section. It is used to collect information on the usual frequency and quantity of consumption of each food in the list for a specified period. A comprehensive food list is desirable whenever possible as it is often impossible to anticipate at the beginning all the questions regarding diet that will appear important at the end of the study. It is designed to be self-administered; however it can be completed by an interviewer. A FFQ is not usually used to collect detailed information on characteristics of foods, such as methods of cooking or the combinations of foods in meals. A FFQ is much better suited for ranking subjects according to levels of food, food groups, or nutrient intake than for providing a measure of absolute intake (1-4). When data from a FFQ are used to estimate relative risks, the degree of misclassification of subjects from their correct quartile of intake is more important than is the quantitative scale on which the ranking is made (5). If nutrient intake estimates are desired, a nutrient calculation software program can be used to calculate them. This is done by calculating the products of the reported frequency of each food by the amount of nutrient in a specified serving of that food, and summing over all foods.

Challenges in using a FFQ are: 1) it may underestimate intake if an incomplete listing of foods contributing significant amounts of nutrients are used; 2) it may overestimate nutrient intakes due to cumulative error from separate reporting of similarly consumed foods (e.g. specific fruits and vegetables); 3) a comprehensive list of foods may increase the length of questionnaire; 4) small amounts of misclassification from the correct level (i.e. quartile) of intake can create a large bias in estimates of associations (6-7); and 5) assessment of nutrients that are variably added to foods in cooking or at the table, such as fats in spreads and sodium in condiments, requires additional questions. Strengths of the FFQ approach are: 1) provides estimates of the respondent's usual intake of foods; 2) designed to be self-administered; 3) can be optically scanned for ease of data entry and analysis; and 4) data can easily be reanalyzed using updated or expanded nutrient or food composition databases. Because the costs of data collection and processing are lower for FFQs than for multiple diet records or recalls (the alternative for obtaining summary estimates of the usual diet), the FFQ is commonly used in cohort studies.

What is the Diet History Questionnaire?

The DHQ to be used in CRIC consists of a food list of 124 items, and also collects limited information about use of dietary supplements. It includes frequency and portion size questions for each food in the list. The DHQ will yield dietary intake data to support hypotheses regarding intake of animal and plant protein, phosphorous, trans fat, and energy consumption in CRI. If desired, data for additional nutrients can be readily obtained for use in future ancillary studies. The food list on the DHQ is based on national dietary intake data, by 24-hour dietary recall, from the 1994-96 US Department of Agriculture's Continuing Survey of Food Intake by Individuals (CSFII). These data were used to decide which foods to include on the DHQ and what the listed portion sizes should be. The DHQ format is based on extensive cognitive research related to how people respond on FFQs and is used at the NCI as the dietary assessment method of choice. The DHQ was designed to be easy to use in a self-administered format, but it can also be interviewer administered, and takes about one-hour to complete. NCI studies to date indicate that response rates with the DHQ are not compromised by its length (8-9). In pilot studies with about 400 individuals in one study and about 1000 in another, the response rates for the DHQ varied from 70-85% (8-9). In both studies, the DHQ response rates were not statistically different than those from shorter FFQs. Numerous cognitive issues in FFQs related to comprehension, order of food items, intake of seasonal foods, intake averages from multiple food items, and format were found and addressed in the DHQ.

Data from two studies conducted to assess its validity show that the DHQ provides reasonable nutrient estimates (9-10). The first validation study showed that most of the cognitive enhancements incorporated in the DHQ were an improvement over the Block questionnaire for frequency response (9). The second validation compared the DHQ with the Block and Willett FFQs, using four 24-hour dietary recalls (one in each season) as reference data (10). The DHQ's performance with respect to relatively validity of nutrient estimates was equivalent to or better than that of the other two FFQs (10). Another NCI-sponsored validation study has been conducted and will provide improved understanding of the extent and nature of error in the DHQ allowing for better interpretation of the DHQ data obtained in CRIC. The Observing Protein and Energy Nutrition Study was conducted from July 1999 to March 2000 and assesses dietary measurement error by comparing results from self-reported dietary intake data from FFQs and 24-hr recalls, with four dietary biomarkers: doubly labeled water and urinary nitrogen, sodium, and potassium (11). Advantages of using the DHQ are that it is public domain, currently supported by the NCI in a package that includes scannable forms, a comprehensive nutrient database, and a nutrient calculation software program. TeleFORM has been used to create a scannable DHQ for use in CRIC.

General comments regarding DHQ

- Be enthusiastic and positive.

Concern regarding the length of the DHQ has been expressed, but some respondents actually enjoy completing FFQs. In other large cohort studies individuals have been willing to complete relatively long dietary questionnaires, probably because of strong general interest in food (12). The DHQ was selected for use in CRIC because we believe it will provide us with useful dietary data to support hypotheses regarding intake of animal and plant protein, phosphorous, trans fat,

and energy consumption in progression of CRI. A comprehensive list of foods is included because it is hard to anticipate at the beginning all the questions regarding diet that will appear important at the end of the study. There are several ancillary studies for which DHQ data will be useful. Our enthusiasm about the DHQ and the value it adds to our study will be transferred to study participants.

- Respondent sensitivity.

A person may be sensitive about what he/she eats. It is critical that the DHQ be checked for completeness in a non-judgmental manner. Please do not express shock when reviewing DHQs. If a response(s) seems questionable, be sensitive in following up with the respondent. For example, you should say: "I see that you have written that you never drink any of the beverages in questions 1 to 10. Is that correct?"

- Estimating portion size and frequency of consumption.

This task may be challenging for respondents. The DHQ has previously been used successfully with the general instructions provided on the front cover (8-9). However, to facilitate greater ease and accuracy of completion, we have recorded a compact disc (CD) for use in CRIC. This audio aid guides the respondent through each section of the DHQ with detailed instructions about estimating portion size, and frequency of consumption. It will also provide assistance with the skip patterns to help reduce the number of missed questions.

- Literacy Issues.

The DHQ can be completed in one hour by those with a grade 12 education. For study participants with low literacy it can be interviewer-administered. It is important to be consistent with the method used. All DHQs for a person should be completed in the same way (interviewer or self-administered) so within- person dietary changes can be examined without possible bias from method of administration.

13.B. Administering the DHQ

General guidelines for administering FFQs have been published (12). The following instructions are specific to administering the DHQ to CRIC participants.

1. Before the screening visit:
    - Familiarize yourself with the general instructions listed on the cover page of the DHQ. They are:
        - Answer each question as best you can. Estimate if you are not sure. A thoughtful guess is better than leaving a blank.
        - Use only a black pen.
        - Be certain to completely blacken in each of the answers.
        - If you make any changes, make an "X" through any incorrect answers.
        - Do not make any stray marks on the form.

        - If you blacken NEVER or NO for a question, please follow any arrows or instructions that direct you to the next question.
    - Fill in the boxes on the bottom, right-hand section of the cover page with the participant's CRIC ID number.

2. At the screening visit:
    - Materials needed are:
        - DHQ form
        - Instructions sheet
        - CD
    - Give the DHQ, CD, and instructions sheet to participants and ask them to return the DHQ and CD at the baseline visit. The instructions emphasize:
        - DHQs should not be folded, frayed or curled.
        - If an error is made, a line should be made through the incorrect answer. Do not scratch out errors. Do not use corrective fluid or white-out.
        - No marks should be made along the bottom or sides of the form.
        - The general instructions on the DHQ cover page should be reviewed and participants should be encouraged to listen to the CD for additional information on estimating portion size and frequency.
3. At the study visit:
    - Check the DHQ for completeness and errors:
        - Check that a black pen was used.
        - Check that there are no blank pages.
        - Check that follow-up questions are answered.
        - Check that there are no double marks where only one answer is permitted.
    - Those participants who do not return the DHQ should be encouraged to fill it out and mail it in. In the event the mailed DHQ was lost, additional DHQs and postage-paid envelopes will be available at the clinic. A follow-up call to participants who have not returned the DHQ within 10 days of issue may be necessary.
    - If the visit is cancelled, the participant should be encouraged to complete the DHQ and mail it along with the CD to the study office. If the visit is rescheduled, the participant should bring the DHQ and CD to the study visit.
4. Before 24 and 48 month follow-up visits:

- The DHQ and CD should be mailed ten days before along with a cover letter to each participant. Again, participants will be asked to return the DHQ and CD at the study visit.

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14. Appendix F: ECHO Procedures

15. Appendix G: EBT Procedures