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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 University of Maryland	Baltimore, MD
Case Western Reserve University University Hospitals of Cleveland Metrohealth Medical Center	Cleveland, OH

NAME	LOCATION
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	PRINCIPAL 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: 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 43-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

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.

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

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.

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).

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

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.

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 it 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.

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 defines the period of time during which a visit is considered on time. Every effort should be made to conduct study visits at regular intervals.

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								

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. Prescreening Data Entry Procedure

The following adjustments to the prescreening procedure have been approved.

Effective Date: July 17, 2003

Process for Completing the Prescreening CRF [PRESCR]

All Participants must have a Prescreening form. The entire form must be completed in writing. The following information addresses the data entry process.

- Form is single entry ONLY.
- Form must be entered into the Data Management System [DMS] on or before the Screening Visit.
- If a participant refuses the prescreening contact, enter only Q1 in the DMS.
- If a participant agrees to the prescreening contact, enter only Q1 - 6 and Q12 in the DMS. [If a participant is eligible, enter no additional data.]
- If a participant is ineligible, enter only the question between Q7 and Q11 that excluded them.

3.B.2. 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.3. 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	Baltimore, MD
03	02	University Hospitals of Cleveland	Cleveland, OH
03	03	Metrohealth Medical Center	Cleveland, OH
03	04	Cleveland Clinic Foundation	Cleveland, OH
04	01	University of Michigan at Ann Arbor	Ann Arbor, MI
04	02	St. Johns Health System	Detroit, MI
04	03	Wayne State University	Detroit, MI
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	Oakland, CA
07	02	University of California, San Francisco	San Francisco, CA

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 immunosuppressive 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) or in a research study that adds significantly to the participant's burden, Examples of studies that would preclude participation in CRIC are the AASK cohort or KEEP Study. (Amendment 1)
- Based on the assessment of the investigator, study coordinator or designee, participant appears unlikely or unable to participate in the required study procedures
- Pregnant women (Amendment #2)
 - ◆ Women who are pregnant based on urine HCG test will be excluded from the CRIC Study. In addition, women who are screened and enrolled in the cohort study (defined as experiencing the baseline visit) and who subsequently become pregnant will not have physical measurements performed or questionnaires

administered during clinical follow-up visits. Administrative forms and the EVENTS data collection form should be completed. If a woman is found to be pregnant after screening but before the baseline visit occurs, she will be withdrawn and can be re-screened approximately one year later.

3.C.3. Additional Exclusion Criteria for Participants Undergoing ¹²⁵I-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 ¹²⁵I-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 in consultation with the PI and is based on criteria listed above.

3.C.4. Additional Exclusion Criteria for EBT/MSCT Testing

Participants who meet the following conditions will be ineligible for the EBT section of the subcohort:

- Weight in excess of 300 pounds or 136.2 kgs.
- CABG, angioplasty or coronary stenting prior to enrollment as indicated on the Medical History Questionnaire and the revised Eligibility form.

3.D. Screening Visit [Visit 2]

Activities and Procedures:

Informed consent process
 Eligibility assessment
 Blood draw [10 cc] and urine test
 Blood pressure measurement
 Height and weight
 Urine Pregnancy test (for all women of childbearing age)
 Instruction: Diet History Questionnaire [DHQ] and
 24 Hour Urine Collection

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.
- Height and weight are also measured at this time and recorded on the ELIG form. Participants weighing more than 300 pounds are not eligible to have an EBT/MSCT test .
- 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, 4, 4a and 4b 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, 4, 4a and 4b 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."
 - Participants will be evaluated and selected for subcohort tests independently based on the I-GFR and MSCT/EBCT eligibility criteria. The DMS will evaluate the responses on the ELIG form and return the subcohort test status to the RC in the ASSIGN module.
 - 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. Cohort Eligibility

Cohort eligibility is evaluated independently from the two subcohort sections for I-GFR and EBT/MSCT testing.

3.E.2. Subcohort Selection and Testing

In 2006, the subcohort selection scheme to determine participant eligibility for subcohort tests (GFR and cardiac CT/EBT) was revised. Originally the determination for subcohort selection and the paired tests was made based on GFR criteria. If a participant was eligible for GFR testing (and selected based on the statistical subcohort sampling schema), a participant was scheduled to receive GFR testing at the Baseline, Year 2 and Year 4 Visits, and cardiac CT/EBT testing at Year 1 and Year 4 visits. It has since been determined that participants who have had Coronary Artery Bypass Graft (CABG) surgery, coronary stenting or angioplasty should be excluded from cardiac CT/EBT testing, based only on the visible changes introduced by these procedures and the potential to compromise the representativeness of the subcohort. For the rest of the enrollment period, evaluation for subcohort testing procedures will occur separately. This will require re-evaluating the cohort

for participants who may be eligible for cardiac CT/EBT testing based on these criteria only, contacting participants who were not originally selected in the subcohort to receive cardiac CT/EBT testing and requesting that they participate in that aspect of the CRIC Study.

The possibility of being selected for both tests is described in the Informed Consent Form and explained during the informed consent process. The protocol changes described are in terms of the changes to the test schedule and subcohort selection probability. The changes do not pose additional risk to CRIC Study participants.

3.E.3. 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.4. 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	4	5	6	7	8	9	10	11	12	13
MONTH	Baseline	6	12	18	24	30	36	42	48	54	60
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
- Medical Event Information
- Blood draw [130 cc]
- Collect 24 hour urine sample
- Collect “clean-catch” urine sample (100 cc) (Amendment 2)
- 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]

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.

- If a participant is known to have a low hemoglobin, the investigator may choose to defer enrollment or draw baseline blood samples during two separate visits.
- If a problem arises with the blood draw, it may be best to try to collect the blood samples later in the same visit or during an additional visit if the participant is willing. The minimum blood draw amount is 65 cc which includes the following:
 - ◆ 3 X 10 ml Tiger Top tubes
 - ◆ 2 X 5 ml Purple Top tubes
 - ◆ 2 X 10 ml Purple Top tubes
 - ◆ 1 X 5 ml Blue Top tube
- All specimens (blood, urine, nails) from participants should be collected, even if the three month window has elapsed and/or the occurrence of lab errors, scheduling problems or a participants' inability to provide all samples during the baseline visit.
- 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. Subcohort Procedures

3.G.1. Preparing Participants for GFR Testing

Participants should be provided the GFR Instruction Sheet. The coordinator should contact the subcohort participant one or two days before the scheduled GFR test to remind the participant of the following details:

- Participants should be well hydrated before the test and encouraged to drink 1000 ml of water the evening before the GFR test.
- On the morning of the test, a participant should drink 5ml/Kg of body weight before arriving at the test center. If a participant is fluid-restricted they should inform the coordinator.
- Participants should be reminded that the test may take up to 3 – 4 hours to complete. The procedure should be thoroughly explained.
- A participant may have a light pre-test meal, containing less than 10 grams of protein. See Appendix D for examples.

3.G.2. EBT/MSCT Guidelines

Guideline for scheduling EBT/MSCT scans for subcohort participants:

EBT/MSCT tests should be performed by technicians who are familiar with the CRIC scanning protocol and have a study Tech ID#.

Female participants must have a urine pregnancy test to confirm that they are not pregnant. Participants who have undergone Angioplasty, Cardiac Stenting and/or Coronary Artery Bypass Surgery (CABG) should not undergo repeat EBT/MSCT testing. Eligibility should be re-reviewed at each subsequent visit. If the subject is found to be permanently unable to undergo EBT/MSCT testing the EBTSTAT form should be completed.

In addition, participants who weigh more than 300 pounds (or 136.2 Kg.) may not be able to be scanned because of limitations of the scanner. As scanners may differ, the exact capacity of the scanner must be known when scheduling subcohort participants. Participants should report their most recent weight.

All information must be recorded on the CTECH form, including complete tech contact information so that the reading center can contact the tech who performed the test in the event of transmission or procedural problems.

3.G.3. Follow-up of Subcohort Participants

It is preferable to collect subcohort test data late, than to not collect it at all. If a participant has been difficult to schedule for follow-up tests, work with them to find the time that will suit their convenience, rather than miss the opportunity to conduct a GFR or EBT test. Whenever possible, schedule tests at approximately the same interval as would occur under ideal conditions. In the event that the baseline EBT/MSCT was obtained late, if the baseline test was done after year 2 (V7), the follow up EBT/MSCT should be completed at year 5 (13). In the event that the baseline EBT/MSCT was obtained late, if the baseline test was done after

year 2 (V7), the follow up EBT/MSCT should be completed at year 5 (V13). In the case of a late baseline iGFR completion, subsequent testing should be done with at least one year between baseline and follow up iGFR testing.

IMPORTANT NOTE: Participants who begin dialysis should no longer have I-GFR testing if they have been part of this subcohort testing group. A GFRSTAT form should be completed to indicate that they are to be removed from this substudy.

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

Activities and Procedures:

Contact Information Update

Concomitant Medications (collected at the 6 Month contact only)

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.I. 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.I.1. Follow-up Visit Guidelines

If a participant is unwilling to continue participating in the CRIC Study, it is suggested that the coordinator try to engage the participant in the aspects of the study that can be accomplished during a brief visit or over the course of two visits.

- Home visits are not recommended for Baseline and Year 1 visits. A home visit can be considered for the Year 2 visit and thereafter if a participant is unwilling or unable to travel to the clinical center and some data and physical measures can be collected.
- If a participant is pregnant during an annual follow up visit, do not collect questionnaires or physical measures. Do collect EVENT information and administrative contact

information. Pregnant participants should resume all CRIC follow-up procedures during the next annual visit.

- If a participant is not willing to complete questionnaires, they may be mailed and completed at home. It would be helpful to provide a self-addressed stamped envelope to return the forms to the clinical center.
- Off site visits can be completed per the off site visit MOP Appendix H. It should be noted that off site visits are only permitted after the year 1 (V5) is completed.

3.1.2. 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 “clean-catch” urine sample (100 cc) (Amendment 2)

Collect nail specimen

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

Concomitant Medications

ECG

EBT [Schedule for Subcohort only]

Questionnaires: Symptom List, Kidney Disease Quality of Life

Echocardiogram [Schedule]

Cardiomyopathy Questionnaire [KCQ] (Amendment 2.)

This is the first time this form is completed.)

- 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 on time window for scheduling these tests are minus and plus two months of the target date. Late visits may be completed until the window for the year 2 (V7) window opens, with the next annual visit to be performed at the end of the on time window target date plus two months.

3.1.3. 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 "clean-catch" urine sample (100 cc) (Amendment 2)

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, Cardiomyopathy Questionnaire [KCQ] (Amendment 2)

3.1.4. 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 “clean-catch” urine sample (100 cc) (Amendment 2)
Collect nail specimen
Physical measures: Blood pressure, Ankle Brachial Index, Anthropometry, BIA
Concomitant Medications
ECG
Questionnaires: Symptom List, Kidney Disease Quality of Life, Cardiomyopathy Questionnaire [KCQ] (Amendment 2)

3.1.5. 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 “clean-catch” urine sample (100 cc) (Amendment 2)
Collect nail specimen
Physical measures: Blood pressure, Ankle Brachial Index, Anthropometry, BIA
Concomitant Medications
ECG
ECHO [Schedule]
EBT [Schedule for Subcohort only or those selected to expand the number of participants in the subcohort as notified by the SDCC.]
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, Cardiomyopathy Questionnaire [KCQ] (Amendment 2)

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

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 clinic visit. A visit will be considered late if it occurs later than the 2 month window after the expected date. However, the RC should continue to attempt to complete this visit information up to 10 months after the anniversary clinic visit date. After the 10 month time window, the next visit window will begin and the RC should apply the clinic visit number of the next appropriate clinic visit. It is preferable to collect as much information as possible, even if this information is collected in the 'late' window, than to miss the opportunity to complete tests and questionnaires.

A visit is considered "late" when it is conducted outside the original window dates. A clinic visit is considered "missing" if it does not occur before the next clinic visit window has opened. Once the next clinic window opens if the prior visit has not been completed, a missed visit form must be completed (MISSVST).

For example, if the patient misses the year 1 visit window, but can come for a clinic visit at 19 months, that will be counted as a Year 1 visit, and the relevant Year 1 visit data should be obtained. But if patient can come at 23 months, then the Year 1 visit will be considered "missing" and the Year 2 data should be obtained. The patient is now in the window for the Year 2 visit.

Another example: If a patient misses a Year 1 visit, but when contacted over the phone for 18 month visit, is able to come in, an in person visit should be scheduled and Year 1 visit data should be obtained. The phone visit information need not be obtained separately in such circumstances, since the materials for the phone visit will be covered by the in person visit.

STUDY VISIT	VISIT DATE	ON-TIME RANGE		ALLOWED, BUT LATE	INFORMATION
Visit 1	Prescreening Visit	May 1, 2006	---	---	There are no time limits on the period between Prescreening and the Screening Visit
Visit 2	Screening Visit	May 20, 2006	---	---	Baseline visit must be completed within 3 months of the Screening Visit date.
Visit 3	Baseline Visit	June 15, 2006 **	Up to Aug. 20, 2006	Up to Aug. 20, 2006	**Calendar tool will calculate all subsequent dates and windows starting with June 15, 2006
Visit 4	6 Month Telephone Follow-up	Dec. 15, 2006	Oct. 15, 2006 to Feb.15, 2007	Feb. 16, 2007 to Apr. 14, 2007	The phone call window is 2 months before and 2 months after the expected date.
Visit 5	Year 1/12 Month Clinic Follow-up	June 15, 2007	Apr.15, 2007 to Aug.15, 2007 [- /+ 2 months]	Aug. 16, 2007 to Apr. 14, 2008 [- 2months, + 10 months]	In this example, visits conducted between Aug. 16, 2007 and Apr. 14, 2008, will be considered 'late.' If Visit 5 has not been conducted by Apr. 15, 2008, it is considered a missed visit.
Visit 6	18 Month Telephone Follow-up	Dec. 15, 2007	Oct.15, 2007 to Feb. 15, 2008	Feb. 16, 2008 to Apr. 14, 2009	The phone call window would be between months 16-20.
If Visits 5 and 6 have not been completed...			...Every attempt should be made to conduct Visit 5 until month 22. If after 22 months, the participant can be scheduled for a clinic visit, a Year 2 visit should be conducted.		
Visit 7	Year 2/24 Month Clinic Follow-up	June 15, 2008	Apr.15, 2008 to Aug.15, 2008 [- /+ 2 months]	Aug. 16, 2008 to Apr. 15, 2009 [- 2months, + 10 months]	The visit window begins at month 22 and continues until month 34. If Visit 7 has not been conducted by month 34 it is considered a missed visit. If after 34 months, a participant can be scheduled for a clinic visit, the data collected will be reported for Year 3, Visit #9.

4.B.2. Participant Retention

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 begins. For participants that are outside of their on-time range, each phone contact should be used as an attempt to schedule the participant for the pending clinic visit. Once the next clinic visit window has opened, the information should be applied to the corresponding on time clinic visit window. The new guidelines for conducting clinic visits are +/- 2 months the scheduled visit date for an "on time" clinic visit or +10 months post the visit window for the "late" visit.

4.B.3. Priority Data Collection Procedures During Follow-up Visits

Ideally, all CRIC Study data can be collected during one comprehensive visit but there are situations during which this is not always possible such as a participant's inability to physically endure an extensive clinic visit, hospitalization, or transportation problems. In such

a situation, if it is necessary to choose which data to collect in a limited amount of time, the following list serves as a guideline to priority data collection during follow-up visits.

First Priority:

Patient contact information (PT CONT)

Health care provide (HP CONT)

Blood pressure (BP CRF)

PHYS ASSESS (WT only)

Medical events (EVENTS)

Medical history (MEDHX)

Draw blood in the following order:

1 Red Gray Tube (Marble-top)

1-10 ml Red Top

2-10 ml Tiger Top

1-5ml Blue Top

1-5ml purple Top

2-10ml Purple Top

Second priority (within this category, not arranged in order of priority):

24 hour urine

ECG

Pulse wave velocity baseline, yr 2 and yr 4

PHYS ASSESS---BIA/ABI, GIRTH, HT

PHYS ACT

KDQOL questionnaire

KCQ questionnaire

BDI-Beck Depression Inventory

Spot urine for proteomics

NSPEC-nails

DHQ-Diet questionnaire

**Third Priority: Requires separate scheduling
(within this category, not arranged in order of priority):**

GFR-usually needs prior scheduling

(if in sub cohort-done Yr 1 and Yr 4)

ECHO (if pt is Yr 1 and Yr 4)

MSCT or EBCT (if in sub cohort-done Yr 1 and Yr4)

4.C. Participant Withdrawal

The RC will complete a **Withdrawal [WITHDR]** case report form when a participant completes their final study visit (Visit 13) **or** at any time before the final 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.

Participants have the right to request that their stored specimens be destroyed at any point in the study or at withdrawal. 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 as well as the Consent Withdrawal (CONWITHDR) case report form. A copy of the Consent

Withdrawal (CONWITHDR) case report form will also 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.

When the participant completes the final study visit (Visit 13) or withdraws from the study, Participant Close-out (PTCL) is the last case report form that should be completed by the Research Coordinator and the Principal Investigator. By adding their signatures to PTCL, the Research Coordinator and the Principal Investigator verify that the data collected and the processes administered to the participant were according to the CRIC study protocol.

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. It is the responsibility of the transferring and receiving site, to maintain communication regarding participant data QA as well as management of the subject when noted on the quarterly site monitoring reports.

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.

4.E. Home Visit Guidelines

The Off Site Visit MOP contains the guidelines for conducting visits outside of the clinic setting such as in the home. This MOP is available as Appendix H of this MOP.

4.F. Tracking Participants Lost to Follow-up

The DCC will generate a list of participants expected for annual clinic visits whose visit did not occur and is not documented in the DMS. This will be distributed to sites for review. Sites will respond as to reason why a visit was missed using coding system included with the report. The DCC will update this information and track it. The log will be reviewed on a monthly basis by the Retention and Recruitment Committee. A participant is only removed from the lost to follow-up spread sheet once the visit occurs, a study stop, withdrawal, or death form is entered or the window has expired for the absolute last possible time for the visit to occur (and that time is 2 months prior to the next scheduled annual clinic visit.)

4.F.1. Deceased Participants

If it is discovered that a participant has died, the Participant Closeout (PTCL) form and WITHDRAW forms must be completed, following all directions. In addition, the EVENTS form should be completed indicating that the participant has died (Question 4), attempting to collect as much information as possible from the reporter of this information.

4.G. Change of Subcohort Status

4.G.1. I-GFR Change of Status

A case report form (**GFRSTAT**) is developed to record a change in the status of a participant who is assigned to the GFR sub-cohort testing after the screening visit but has since either changed his/her mind or it has been determined that the participant is ineligible to continue with the testing. A change in status permanently removes a participant from participating in the GFR sub-cohort testing and should be applied after much consideration. Details on the completion of the case report form are available in Chapter 5.

4.G.2. EBCT/MSCT Change of Status

A case report form (**EBTSTAT**) is developed to record a change in the status of a participant who is assigned to MSCT/EBCT sub-cohort testing after the screening visit but has since either changed his/her mind or it has been determined that the participant is ineligible to continue with the testing. A change in status permanently removes a participant from participating in the MSCT/EBCT sub-cohort testing and should be applied after much consideration. Details on the completion of the case report form are available in Chapter 5.

4.H. CRIC Plus: Participants Who Advance to ESRD

CRIC Plus is an extension of the core CRIC protocol that involves all seven clinical centers. The EVENT CRF indicates those participants who have a kidney transplant or begin dialysis. For these participants, the RRT Primary and RRT Follow-up forms must be completed.

In addition, an algorithm will be applied to the most recent creatinine value to estimate if a participant is approaching advance CRI, which is defined as eGFR < 20 ml/minute.

See Appendix H for the complete CRIC Plus manual.

5. Data and Administrative Forms

5.A. Case Report Forms

5.A.1. Acquisition of Case Report Forms from the Scientific Data Coordinating Center (SDCC)

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

5.A.2. Printing Case Report Forms with Complete Header Information

Directions to access case report forms with automated header entry:

Case report forms currently available in the Data Management System require Adobe Acrobat version 5.0 or higher, to use the automated header information function.

[If your system has Adobe Acrobat 5.0 installed already, you do not need to download the software. If your system does not have version 5.0, Adobe Acrobat 6.0 is available on the CRIC study website for download to your computer. This can be done by clicking on the link and following directions or contacting your local IT person for assistance.]

To print case report forms from the Forms module in the Data Management System:

- Log in using your username/password.
- Click on Forms and Reports button.
- Click on Case Report Forms button.
- Select and click on a visit packet or individual data or administrative case report forms needed for the CRIC study visit.
- HCRIC study case report forms are available exclusively for participants enrolled in the Hispanic CRIC ancillary study.



Chronic Renal Insufficiency Cohort Study
Case Report Forms
Please click any of one of the buttons below:

Data Entry CRF Forms
Administrative Forms
Blank Study Reports
HCRIC CRF Forms
Visit Packet for Visit 01
Visit Packet for Visit 02
Visit Packet for Visit 03

- Case report forms within a packet are arranged in the order of required case report forms for the visit, administrative case report forms and as-needed case report forms.
- Electronic headers are designed for the header information on the case report forms to minimize errors in key identifiers.
- They allow header information to be populated in similar cells across (multiple) linked pages.
- Header information can be completed manually or electronically.
- For electronic headers, enter header information, including Participant ID, Initials, etc. on the first page, using the tab key to move from one field to the next one.
- Each page within the packet will be populated with this information.
- Print case report forms.
- Print function allows you to print select pages by specifying the range.
- Two buttons in the header are available to reset partial or all header information:
- Partial reset, indicated by “Reset Patient/RC”, allows Participant ID, Initials, RC ID to be cleared for a new participant, while CCID, Site and CRF Date remains populated from the previous entry.
- “Reset All” clears the header information previously entered, to allow entry for new information.



Participant ID:	<input type="text"/>	Participant Initials:	<input type="text"/>
Clinical Center:	<input type="text"/>	Site:	<input type="text"/>
CRF Date:	<input type="text"/> / <input type="text"/> / <input type="text"/>	Visit Number:	<input type="text"/>
		RC ID:	<input type="text"/>

- Header information for single case report forms (data or administrative) is entered on each case report form individually prior to printing.
- A multiple page case report form, e.g. Medical History (*MEDHX*) or Mini Mental State Exam (*MMSE*), requires header information on page one only. Subsequent pages are populated based on the header information on the first page.
- Header information entered prior to exiting the visit packet or an individual case report form must be cleared for the next user.
- In case of inadvertent saving of the header information from a previous use, populated data can be cleared by clicking on the “Reset All” button.

5.A.3. General Instructions for the Completion of Case Report Forms

5.A.3.a) RC ID Number and Tech ID Number

- Two different types of identifiers are used in documenting CRIC study procedures:
- RCID (part of the header information) identifies the person who completes a case report form.
- The SDCC must be notified of the new RC ID when a new staff member joins the CRIC study team at the site.
- Tech ID indicates the person who performs a specific measure for a CRIC study participant who may be external to the local CRIC study

group, such as an echocardiogram or a Computed Tomography (CT)/Electron Beam Tomography (EBT) technician.

- For physical measures, Tech ID may be the same as RC ID.

It is important to provide the SDCC Project Managers and the associated Reading Centers complete contact information for all project personnel to properly identify them in the Data Management System for Quality Assurance purposes and to be contacted by Reading Centers, if necessary.

5.A.4. General Instructions for all Case Report Forms

- Two types of case report forms are used for the CRIC study:
- Data case report forms contain participant data and are entered in the database.
- Administrative case report forms are used for CRIC study organization and not entered in the database.
- A case report form is a data entry case report form unless it is identified as "Administrative" directly under the title at the top of the page.
- The Research Coordinator (RC) should check the case report forms in a packet against the Recruitment Chart (**CHART1**) or Clinic visit Chart (**CHART2**) to confirm that all case report forms are available before a clinic visit or telephone contact with the participant.
- Missing case report forms in a visit packet should be printed from the website or the Data Management System prior to the visit.
- As case report form changes occur, CRIC study sites will be notified and current versions of case report forms will be made available on the website and the Data Management System.

General instructions:

- All case report forms should be completed in black ink; do not use pencil or blue ink.
- Responses should not be left blank; missing responses should be noted on the Comments Sheet (**COMM**).
- If the participant is unsure of a response, (s)he should use his/her "best estimate" rather than leave the question unanswered.
- To code dates where only partial responses are available (e.g. month and year or year only), the sites can decide on a convention for coding the missing information (e.g. 01 for month, 01 for day).
- It is important that the site Research Coordinator informs all data collectors involved in data collection of site-specific conventions.
- It is important that the Research Coordinator completes the header information before administering case report forms to insure easy identification in case of separated pages, or multiple participant visits in a day.
- Participant ID number is determined on the site-specific Participant ID Log (**PTIDLOG**) during the screening process.
- The Research Coordinator is responsible for reviewing all completed case report forms.
- All personal identifiers should be obscured or "blacked out" from copies of laboratory results, procedure reports and other source documents sent to the SDCC.
- Study identifying information and Participant ID and Participant Initials should be recorded prior to forwarding copies to the SDCC, if requested.
- All original copies should retain personal identifying information.

Participant completed case report forms:

- These case report forms are self-reports, and are completed by the participant.
- The Research Coordinator should be available to the participant for questions or clarifications.
- The Research Coordinator may administer questionnaires to the participant if and when it becomes apparent that the participant has reading or comprehension issues.
- If a self-reported questionnaire is administered to the participant at the baseline visit, at subsequent clinic visits the questionnaire must also be administered to the participant to maintain consistency in administration.
- For each participant completed case report form, the Research Coordinator should check the appropriate box to indicate whether case report form was self-administered or interviewer-administered.
- In the event that the participant is unable to complete the forms, forms may be administered by proxy. Study staff should complete the PROXY CRF and follow local guidelines regarding proxy data collection.
- Since the participant may find some of the information on the case report forms to be sensitive, whenever possible, the participant should be encouraged to complete the case report forms unassisted.
- Before the participant leaves the clinic, the Research Coordinator must review the case report forms for legibility and completeness.
- After the Research Coordinator reviews the case report forms, the Research Coordinator should note his/her RC ID number in the header.

Research Coordinator completed case report forms:

- These case report forms are not completed by the participant, but are administered to the participant by the Research Coordinator, by interviewing the participant on specific questions on the case report forms.
- The Research Coordinator is responsible for getting an appropriate response from the participant if the participant's response is unclear, incomplete, or irrelevant.
- The Research Coordinator should use "probing" techniques to refocus and redirect the participant's attention to the question to elicit the best possible response.
- The Research Coordinator 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).
- The Research Coordinator should demonstrate understanding and patience at all times, as some questions addressed in the case report forms 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 the importance of the question and the process in place to maintain confidentiality of his/her response.
- All case report forms to be completed by the Research Coordinator (or occasionally the Principal Investigator) should be completed during the visit unless awaiting a report (e.g. laboratory results).
- The Research Coordinator should review the case report forms for completeness and legibility before the participant leaves, in case additional information or clarification is needed.

Review of completed case report forms:

- The Research Coordinator should review all case report forms for legibility, accuracy, and completeness before they are entered into the database.

- If the Research Coordinator identifies an error while reviewing the case report forms, the error should be corrected on the completed case report form by crossing out the error with a single line in black ink, entering the correct information and initialing and dating the change.
- The Research Coordinator should circle the correction for clarification, if necessary.

5.A.4.a) Time frame for completion and data entry of case report forms:

- The time frame for completion and data entry of case report forms is two (2) weeks from the date of collection.
- Due to the type of the information contained in these case report forms, Immediate Alert (**ALERT_I**), Urgent Alert (**ALERT_U**), and Computed Tomography Alert (**ALERT_CT**) must be completed and data entered as soon as possible.

5.A.4.b) General Coding Issues:

- Date fields are entered in the “mm/dd/yyyy” format with the year recorded as 4 digit number (e.g. 1997, 2001).
- Time is recorded in the 24-hour clock format (e.g. 1:00 pm is recorded as 13:00 hours).
- Data fields have units of measurements and spaces available, where applicable, to capture accurate values (e.g. ___ / ___ mmHg for blood pressure; __ years old).

Header Information:

Participant ID is determined by the Research Coordinator and logged in the Participant ID Log (**PTIDLOG**) at each Clinical Center and Site.

- Participant ID is an eight–digit (8) number with a separator after the second and the fourth digit for Clinical Center ID and Site ID.
- The first two (2) digits represent the Clinical Center ID.
- The next two (2) digits represent the Site ID.
- The last four (4) digits are sequential numbers, starting with 0001, assigned to each potential participant (e.g. 0002, 0003) who verbally consents at prescreening contact (Visit 1).
- Once assigned, a participant ID is not deleted or transferred to another CRIC study participant.

Clinical Center (CC) is a 2-digit number that identifies the primary recruiting center.

- CC IDs are unique and are 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

Site is a two (2) digit ID that is 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) 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**

Participant Initials are the first letter from each of the participant’s first, middle and last name, 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 = JXS).
- Participant initials at the time of registering the participant in the Data Management System will be maintained for the duration of the study and will not be subjected to edits.

Visit Numbers are applied to prescreening, screening, baseline and follow-up visit contacts that are identified in the protocol for specific events that occur during the course of the CRIC study. These contacts have been translated into visit numbers:

Prescreening contact	Visit 1
Screening visit	Visit 2
Baseline visit	Visit 3
Six (6) month phone clinic visit	Visit 4
Twelve (12) month clinic visit	Visit 5
Eighteen (18) month phone clinic visit	Visit 6
Twenty-four (24) month clinic visit	Visit 7
Thirty (30) month phone clinic visit	Visit 8
Thirty-six (36) month clinic visit	Visit 9
Forty-two (42) month phone clinic visit	Visit 10

Forty-eight (48) month clinic visit	Visit 11
Fifty-four (54) month phone clinic visit	Visit 12
Sixty (60) month clinic visit	Visit 13

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

RC ID is a 4-digit number to identify a Research Coordinator at a specific site, who completes visit-specific assessments.

5.A.5. Specific Instructions for Data Case Report Forms

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

5.A.6. Data Case Report Forms:

(ALERT_CT) - Computed Tomography Alert

Purpose: This case report form reports potential serious medical problem(s) or emergency(s) based on clinical observation and reported CRIC study information, on a Computed Tomography/Electron Beam Tomography scan at the Computed Tomography Reading Center, and appropriate disposition of the problem at the CRIC site.

The site Research Coordinator and/or Principal Investigator must report results and outcomes to the participant's primary care physician for clinic visit.

Who: Completed by Computed Tomography Reading Center personnel, Research Coordinator and/or the Principal Investigator.

The Computed Tomography Reading Center will contact the Principal Investigator and the Research Coordinator directly for alerts observed in Q1c (large pericardial effusion), 1d (aortic aneurysm) and 1e (aortic valve calcification).

When: This case report form is completed on an "as needed" basis.

Directions: When the participant undergoes Computed Tomography/Electron Beam Tomography at a clinic visit, the scan(s) is sent to the Computed Tomography Reading Center.

Specific alerts have been identified in the protocol. When Computed Tomography scans are read at the Computed Tomography Reading Center, the Reading Center identifies the alerts in Q1c, 1d and 1e, and checks other appropriate actions taken in Q2a and Q2b of the ***ALERT_CT*** case report form. The completed case report form is faxed to the site Research Coordinator/Principal Investigator.

When the site receives this alert from the Computed Tomography Reading Center, the site Research Coordinator and or the Principal Investigator is responsible for checking an appropriate response in Q2c (Primary MD notified) and entering the case report form data in the Data Management System.

Note: Completion of an ***ALERT_CT*** case report form may require a Medical Events (***EVENTS***) investigation/confirmation.

ALERT_CT is available in the Data Management System as a “single case report form”, indicating “as-needed” data collection and entry. One case report form entry is allowed per visit.

(ALERT_I) - Immediate Alert:

Purpose: This case report form reports potential serious medical problem(s) or emergency(s) based on clinical observations or reported CRIC study information, and appropriate disposition at the CRIC site.

The site Research Coordinator and/or Principal Investigator must report results and outcomes to the participant’s primary care physician.

Who: Completed by the Research Coordinator and/or Principal Investigator.

When: This case report form is completed on an “as needed” basis upon identification of immediate alert information associated with CRIC study clinic visits and tests.

BP alerts are based on observations by the Research Coordinator during blood pressure readings.

Acute distress may be reported by the participant to the Research Coordinator or the Principal Investigator at the time of the CRIC study visit.

Echocardiogram alerts are based on clinical observations and/or reading from the test administered to the participant.

Directions: Specific alerts are identified in the protocol and may be encountered at the time of a clinic visit. When reporting such events, the Research Coordinator may need to check “Yes” for only a few alerts/items listed on the case report form. Remaining alerts not encountered at the time of the exam by the Research Coordinator must be checked appropriately as “No”, “N/A” or “Not Done”. Items cannot be left unanswered.

Values or observations that constitute an alert are available on the case report form for reference.

Q1: The date of alert should indicate the date of CRIC study visit when a clinical observation, classified as an alert in the protocol, is made.

Q2a-b: Blood pressure reading, where systolic pressure is > 180 mmHg or diastolic pressure is >110 mmHg at a visit, is reported as an alert by checking the “Yes” response.

If both are elevated, Q2a and Q2b should be checked as “Yes” to indicate an alert.

If one of the 2 measures is elevated, the elevated reading is checked “Yes” and the normal reading is checked as “No”.

Q3a-b: Acute distress is restricted to 3 items - chest pain, severe respiratory distress and acute neurological symptoms. Other symptoms determined as acute by the Principal Investigator or the Research Coordinator are noted under “Other” category and specified in the space provided.

All items are checked as “Yes” or “No” based on clinical reporting or observation and cannot be left unanswered.

Q4a-b: The date of the echocardiogram in Q4a is the date the test is administered to the participant at the CRIC study visit. If an echocardiogram is not administered at the visit, “Not Done” is checked and Q4b and Q4bi-vi are left unchecked.

Echocardiogram reading, whether read by the ECHO Reading Center (Central) or locally at the site (Local), is identified in Q4b when an echocardiogram is administered to the participant during the visit. Appropriate response is checked in Q4bi-vi based on the echocardiogram reading.

A false positive reading may be determined by the Principal Investigator based on the availability of the participant’s historical information or by the echocardiographer reading the scan (centrally or locally).

Regardless of where the reading occurred, it is critical to check a response of “Yes”, “No” or “False Positive” for each of the items identified as alerts when an echocardiogram is performed on the participant.

Q5a-d: Responses recorded here indicate the appropriate disposition of the medical alert. The Principal Investigator or the Research Coordinator indicates by checking the appropriate boxes if the medical information was transmitted to the participant’s primary MD through oral and written communication, and if any medical intervention (ER admission, hospitalization) was initiated.

Q6: 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 Research Coordinator and/or the Principal Investigator to inform the participant of the outcome, e.g. echocardiogram results, etc.

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

Completion of **ALERT_I** case report form may require an event investigation/confirmation, and completion of the Medical Events (**EVENTS**) case report form.

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

ALERT_I is available in the Data Management System as a “single case report form”, indicating “as-needed” data collection and entry. One case report form entry is allowed per visit.

(ALERT_U) - Urgent Alert

Purpose: This case report form reports significant abnormal laboratory result or clinical process outcome from the Central Laboratory at the University of Pennsylvania or the Central ECG Reading Center (CERC).

The site Research Coordinator and the Principal Investigator must report results and outcomes to the participant’s primary care physician.

Who: Completed by the Research Coordinator and/or Principal Investigator.

When: This case report form is completed on an “as needed” basis upon identification of urgent alert information associated with CRIC study clinic visit-based laboratory test results and/or electrocardiogram (ECG) reading.

Laboratory tests ordered at a clinic visit, reporting out-of-range or abnormal values as referenced on the case report form, are considered “alerts” and must be recorded on the case report form and entered in the Data Management System.

Electrocardiogram administered to the participant at the clinic visit needs to be reported on the **ALERT_U** case report form if “alerts” are identified. These alerts are recorded on the case report form and entered in the Data Management System.

Directions: The site Research Coordinator should identify and transcribe information from available laboratory results, e-mail alert notification and local electrocardiogram interpretation onto the **ALERT_U** case report form and also note actions taken to inform the participant and his/her primary care physician through oral or written communication.

Specific alerts have been identified in the protocol and may be encountered at the time of a clinic visit. When reporting such events, the Research Coordinator may need to check “Yes” for only a few alerts listed on the case report form. Remaining alerts not encountered at the time of the exam by the Research Coordinator must be checked appropriately as “No”, or “Not Done”. Items cannot be left unanswered.

Specimen collected and electrocardiogram performed at a clinic visit are sent to the Central Laboratory at the University of Pennsylvania and Central ECG Reading Center respectively. Specific alerts have been identified in the protocol for results based on laboratory tests performed at Central Laboratory and the electrocardiogram interpretations. Laboratory value alerts are made available to the sites as soon as possible through the “View Study Alert” module in the Data Management System and by an e-mail from the SDCC. Electrocardiogram alerts are typically available to the sites from their local ECG Centers.

When reporting such results, it may be necessary to check “Yes” or “False Positive” (for electrocardiogram readings only) for one, two or several alerts/items listed on the case report form. Remaining alerts not reported at the visit are checked as “No”. Items cannot be left unanswered.

Q1: Date of the alert is the date the abnormal value is reported by the Central Laboratory or local or Central ECG Reading Center.

Note: The CRF date in the header is the date when the Research Coordinator completes **ALERT_U**.

Q2a-h: Laboratory results, other than those listed on the case report form, determined as abnormal are noted as “Other” and identified in the space provided.

Results identified as “abnormal” are checked “Yes” and normal values are checked “No”.

Each item should have a response and cannot be left unchecked.

Q3a-b: A skip pattern is introduced at Q3a if an electrocardiogram is not performed on the participant. If an electrocardiogram is not administered at the clinic visit, “Not Done” is checked and responses in Q3bi-ix are left unanswered.

Date of reading is the date the electrocardiogram was read to identify abnormalities. If an electrocardiogram is not done at the visit, "Not Done" is checked.

Abnormal findings from a local interpretation of the electrocardiogram are generally noted on **ALERT_U** with a "Yes" or "False Positive" response.

A false positive reading may be determined by the Principal Investigator or the local ECG staff, based on availability of the participant's historical information.

Q4a-b: Responses recorded in Q4a-b indicate the appropriate disposition of the medical alert. The Principal Investigator and/or the Research Coordinator shares information about the medical emergency with the participant's primary MD through oral and written communication.

Q5: The participant may or may not be aware of the abnormal results at the time of the visit. It is the responsibility of the Research Coordinator/Principal Investigator 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** case report form may require an event investigation/confirmation, and completion of the Medical Events (**EVENTS**) case report form.

ALERT_U data is entered and verified in the Data Management System as soon as possible.

ALERT_U is available in the Data Management System as a "single case report form", indicating an "as-needed" data collection and entry. One case report form entry is allowed per visit.

(AMPUT) – Amputation Information

Purpose: This case report form collects specific information on amputation of the leg or foot.

Who: Completed by the Research Coordinator, based on his/her observation(s).

When: This case report form is completed on an "as needed" basis starting with the baseline visit (Visit 3).

Directions: **This is an "as needed" case report form that is completed when the participant reports amputation of the toes or legs on the MEDHX (Qs 23/24) or MEDHXUP (Q 9) forms. It can also be completed if the amputation is obvious at the visit. It provides a cross for the items on MEDHX and MEDHXUP mentioned above.**

Amputation may also be mentioned by the participant when seeking information on Q 3a of the EVENTS case report form.

The case report form consists of the data collection section on page 1 and an anatomical representation of the leg and foot on page 2.

The anatomical representation on page 2 has each area of interest labeled to assist the Research Coordinator in identifying the site and the side of amputation. Based on that, the Research Coordinator fills in the information on page 1 of the case report form.

On page 1, information recorded for the two (2) sides are represented by two (2) columns – the right leg and the left leg. Skip patterns are introduced based on the site of the amputation to record pertinent data.

AMPUT is available in the Data Management System as a “single case report form”, indicating “as-needed” data collection and entry.

(ANCILLRY) – Ancillary Studies – Participation Information

- Purpose:** This case report form collects participation information for the ancillary studies.
- Who:** Completed by the Research Coordinator when a participant, who has complete baseline visit (Visit 3), is enrolled in any of the ancillary studies available to him/her because of participation in the CRIC study.
- When:** This case report form is completed on an “as needed” basis starting with the baseline visit (Visit 3).
- Directions:** A CRIC study participant cannot participate in an ancillary study independent of the CRIC study.

As part of the CRIC study consenting process at the site, a potential participant is also offered participation in ancillary studies. These studies are available to the participant when the participant qualifies for the CRIC study and completes the baseline visit for the CRIC study. Processes in the ancillary studies can occur at the same time as the CRIC study processes.

Each time the participant is enrolled and actively participates in an ancillary study process, the Research Coordinator should complete the Ancillary Information (**ANCILLRY**) case report form by checking the ancillary studies that the participant is enrolled in. “Check all that apply” option allows the Research Coordinator to check multiple ancillary studies at each visit.

ANCILLRY is not a continuous CRF and only one entry of the CRF is allowed per visit. A new ANCILLRY case report form is completed each time the study participant is administered procedures **for the first time** for any of the available ancillaries. It is always associated with a study visit.

ANCILLRY is available in the Data Management System as a “single case report form”, indicating “as-needed” data collection and entry.

(ASSIGN) - Participant Assignment

- Purpose:** Assign a consented and eligible participant to the CRIC study and its sub-cohort– GFR and/or CT/EBT testing, based on age, race, gender, and e-GFR value.
- Who:** Research Coordinator.
- When:** Completed after screening visit (Visit 2).

Directions: Data for ASSIGN is generated by the computer and completed based on the information available on the computer screen.

The following 3 case report forms 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 Data Management System prior to completing Participant Assignment case report form (**ASSIGN**).

Step I – eGFR Value in item #1:

eGFR value is calculated electronically within the eGFR module in the Data Management System on the **ASSIGN** screen, based on data available from entering and verifying **ELIG**, **SCRLAB** and **DEMO**.

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

By clicking on the eGFR button on the **ASSIGN** screen, eGFR value is displayed on the screen. This value is recorded on the **ASSIGN** case report form in item #1.

Participant ID is entered into the eGFR module available on the screen. This generates a eGFR value that is recorded on **ASSIGN** case report form.

Step II – Participant Assignment:

Participant Assignment is 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, 4, 4a and 4b is recorded on **ASSIGN** case report form.

The screen then prompts the Research Coordinator to verify assignment outcome data in item #s 2, 3, 4, 4a and 4b by clicking on the Verification module.

Step III – Outcome:

When the verification process is complete, the Research Coordinator contacts the participant to inform him/her about the CRIC study assignment for GFR and CT/EBT and schedule a baseline visit (Visit 3).

The participant may qualify for participation in one or both assignments (GFR and/or CT/EBT testing) depending on eligibility criteria for the sub-cohort. If the participant is interested in continuing with the CRIC study, the assignment outcome will be discussed with the participant and CRIC study procedures for the sub-cohort will be reviewed and the next visit scheduled.

If, at this time, the participant decides to discontinue participation in the CRIC study, the Research Coordinator completes the Loss of Eligibility for GFR testing (**GFRSTAT**) and Loss of Eligibility for GFR testing (**EBTSTAT**) as well as Withdrawal (**WITHDR**) case report form, checking the primary reason for termination from the CRIC study.

If the participant does NOT qualify for the sub-cohort based on the age/eGFR criteria (Q2 and Q3 are No), or the CT/EBT criteria (Q3 is No), the Research Coordinator completes the **ASSIGN** case report form based on the data displayed on the screen, verify this data by clicking on the VERIFICATION button and inform the participant of the assignment outcome.

Verification is a required step in the assignment process. The participant is not considered to be enrolled in the CRIC study if assignment data is not verified or verification is incomplete. The browser in the Data Management System can assist in verifying the completion of the assignment process.

(BDI) - Beck Depression Inventory:

Purpose: This questionnaire determines depressive symptoms experienced by the participants in the CRIC study.

Who: Participant completed, as a self-report.

When: This case report form is completed at:
Baseline visit (Visit 3)
24-month clinic visit (Visit 7)
48-month clinic visit (Visit 11)

Directions: Beck Depression Inventory is a self-report questionnaire. The participant completes a twenty-one question survey, rating statements expressing feelings they have experienced in the past 7 days 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 Data Management System.

The participant must be instructed to rate his/her feelings in the past 7 days.

Total score is stored in the Data Management System and is not available for recording on the questionnaire.

Q9: Particular attention is paid to the response of “3” on Q9, which suggests that the participant may have suicidal thoughts. The Principal Investigator (or a Principal Investigator designee, a Psychologist or Psychiatrist) should be consulted to verify that the participant is not a danger to him or herself after leaving the site.

An administrative case report form - Beck Depression Inventory Comments Sheet – (**BDICOMM**) is developed to record action taken to assess the safety of the participant who reports suicidal ideation in Q9 (a response of “2 - I would like to kill myself” or 3 – “I would kill myself if I had the chance”).

The Research Coordinator should check responses for completion and legibility.

If the questionnaire is completed with significant assistance from the interviewer, the Research Coordinator should check the appropriate box at the end of the questionnaire.

If the interviewer administers this questionnaire to the participant at the baseline visit (Visit 3) because of reading or comprehension issues, the interviewer must administer the interview to the participant at all subsequent visits to maintain consistency in administration.

BDI data is entered and verified in the Data Management System.

(BP) - Blood Pressure Form:

Purpose: This case report form records measured (seated and standing) blood pressure and pulse.

Who: Completed by the Research Coordinator or designee

When: This case report form is completed at:
Screening visit (Visit 2)
Baseline visit (Visit 3)
12-month clinic visit (Visit 5)
24-month clinic visit (Visit 7)
36-month clinic visit (Visit 9)
48-month clinic visit (Visit 11)
60-month clinic visit (Visit 13)

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

Check the "Not measured" box to explain missing data where applicable, e.g. if the participant is an amputee and blood pressure and pulse cannot be recorded.

Q1: Date noted is the date of CRIC study visit when the blood pressure is measured. If the blood pressure is not measured, check "Not measured" and go to the next process for the visit. If "Not measured" is checked in question 1, subsequent information is not expected.

Q2: Time is recorded on a 24 hour clock.

Q3: Each site should label equipment sequentially and the number used for labeling the site equipment is used for this item.

Q5: A tape measure is used to measure and record mid-point circumference.

Q6: Information available on the cuff of the equipment is recorded for this item.

Q7: This measurement is done while the participant is seated. The pulse is measured for 30 seconds, the reading is multiplied by 2 and the calculation is recorded on the case report form.

Q8-12: Observation is made while the participant is seated and the reading is recorded on the case report form.

If a participant refuses to allow a blood pressure measurement because of physical discomfort, the data field is left blank and a reason is noted in the CRIC study source document.

If systolic or diastolic reading is ≥ 300 mmHg, the Research Coordinator should record a value of 300 mmHg.

Q13: This measurement is done on a standing participant. The pulse is measured for 30 seconds, the reading is multiplied by 2 and the calculation is recorded on the case report form.

If the participant is unable to stand for the assessment due to physical limitations, check "Not measured" to indicate that the standing pulse is not measured.

Q14: Blood pressure is observed and the reading is recorded while the participant is standing.

If the participant is unable to stand for the assessment due to physical limitations, check "Not measured" to indicate that the standing blood pressure is not measured.

Q15: Technician ID is a 4-digit number that identifies the CRIC study site personnel measuring the participant's blood pressure and pulse. This ID is also registered in the Data Management System at the SDCC. This information is used for Quality Assurance purpose for blood pressure measurements in the CRIC study.

Note: Elevated values may generate an immediate alert that should be noted on the Immediate Alert (**ALERT_I**) case report form.

Participants with elevated blood pressure may be on anti-hypertensive medications that should be noted on the Concomitant Medication (**CMED**) case report form.

BP data is entered and verified in the Data Management System.

(CMED) - Concomitant Medications:

Purpose: This case report form records all prescription medications, non-prescription medications, herbal supplements, dietary supplements or vitamins currently taken by the participant in the 30 days preceding a clinic visit contact or a clinic visit.

Who: Completed by the Research Coordinator as an interview.

When: This case report form is completed at:
Baseline visit (Visit 3)
6 month phone clinic visit (Visit 4)
12-month clinic visit (Visit 5)
24-month clinic visit (Visit 7)
36-month clinic visit (Visit 9)
48-month clinic visit (Visit 11)
60-month clinic visit (Visit 13)

Directions: At each clinic visit, including baseline visit (Visit 3) and the first phone contact (Visit 4) the Research Coordinator interviews the participant on his/her use of prescription medications, non-prescription medication, herbal supplements, dietary supplements and vitamins. **CMED** information provided at previous visits is not reviewed against the information recorded at the current visit in terms of data collection for the CRIC study. Instead, the Research Coordinator can use the list from the previous visit to review medications currently used by the participant to help elicit the best possible information from the participant on their medication or supplement use.

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

At baseline visit (Visit 3), 6 month phone visit contact (Visit 4) and at each annual clinic visit thereafter (Visits 5, 7, 9, 11 and 13), any medications (new or on-going) taken in the 30 days preceding the 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 or to the telephone.

Research Coordinator should document the drug name, total daily dose, unit, frequency and route of administration for each medication that the participant reports.

If a participant reports that (s)he is participating in a double-blind clinical trial, the Research Coordinator should record the name of the drug that (s)he may be taking on the **CMED** case report form and explain the details of the trial thoroughly in the CRIC study source document.

Q1-1a: A response must be available in Q1a if the participant's response to Q1 is "Yes".

Q1-1a: If the participant reports taking medications, supplements, etc. in the past 30 days, the number of medications taken are reported in this item. This item facilitates recording medication information in the Data Management System, creating number of records in the database equivalent to the number of medications to be recorded for data entry purpose.

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

Drug Code: Drug code is obtained from the Medication Reference Tool, a module available in the Data Management System that contains a dictionary of drug codes applied to common medications and supplements available in the market.

Every attempt should be made by the Research Coordinator to code the drug from the comprehensive list of medications in the Medication Reference Tool. To find a drug code, the medication name can be typed in using a generic name or a brand name in the appropriate space. Partial name typed in the query box generates a longer list of codes, which in turn assists the Research Coordinator in selecting the right code, if the drug name provided by the participant is misspelled.

If a drug code for a concomitant medication that the participant has recorded is unavailable in the Medication Reference Tool in the Data Management System, the Research Coordinator should call the Clinical Data Manager at the SDCC.

If the Clinical Data Manager is unable to locate the information for the Research Coordinator, 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 at a later date and inform the Research Coordinator of the change.

Medication Name: The Research Coordinator records medication name provided by the participant on the case report form. Based on this information, the Research Coordinator should query the Medication Reference Tool for the drug code.

Unlike the case report form, Medication Name in the CRIC database will be stored as the generic name of the reported medication/treatment, corresponding to the drug code.

Total Daily dose (TDD): The Research Coordinator 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 if Tylenol 3 is reported.

TDD is averaged to a 24 hour period if the participant reports doses that vary from day-to-day on certain medications. For example, a varying dose of insulin reported over a 7 day period can be averaged to a 24 hour period by adding up the doses taken in a week and dividing by 7.

Unit: Select the most specific response possible from the legend available on the case report form.

“Other” is coded when unit does not fall in any of the categories listed in codes 1-10. When coding an “Other” response, additional information is recorded in the CRIC study source document for future retrieval, if needed.

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

“PRN” is coded when a medication is taken on an as-needed basis.

“Other” is coded when the medication frequency does not fall in any of the categories listed in codes 1-5. When coding an “Other” response, additional information is recorded in the CRIC study source document for future retrieval, if needed.

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

“Other” is coded when the route of medication does not fall in any of the categories listed in codes 1-10. When coding an “Other” response, additional information is recorded in the CRIC study source document for future retrieval, if needed.

For participants reporting multiple medications, additional medications are recorded on Concomitant Medications – Additional Page (*CMEDADD*), available in the “Forms” module of the Data Management System.

CMED data is entered and verified in the Data Management System.

(CONWTHDR) - Consent Withdrawal:

Purpose: This case report form documents a participant’s request to withdraw consent for the use of stored specimen(s) or Social Security Number provided for research purposes.

Who: Completed by the Research Coordinator, when requested by patient;
Central Laboratory personnel, if/when the specimens are disposed;
SDCC, when the encryption for the Social Security Number is archived.

When: This case report form is completed on an “as needed” basis.

Directions: **CONWTHDR** documents the participant’s wishes to withdraw their specimen(s) or social security consent. The Research Coordinator must obtain the participant’s signature at the bottom of page 1 for appropriate action to be taken by the Central Laboratory personnel or the SDCC.

Q1a-d: If the participant withdraws consent for the use of Social Security Number only, a “No” response is checked.

Check “N/A” if the participant did not consent to the collection of specimen(s).

Q1e-g: If the participant withdraws consent for the use of Social Security Number only, a "No" response is checked.

Check "N/A" if the specimens were not collected at the visits.

Q2 If the participant withdraws consent for the use of stored specimens only, a "No" response is checked.

Check "N/A" if the participant did not consent to the use of their Social Security Number.

Q3-4: These items are completed by the Central Laboratory and SDCC personnel and the completed case report form is faxed to the site confirming the actions taken.

Comments: Additional information that needs to be recorded by the Central Laboratory or the SDCC to take appropriate actions is noted in this area.

Contact information: This information facilitates the consent withdrawal process at the Central Laboratory and the SDCC.

Note: Do not enter in the Data Management System until Central Laboratory acknowledges the withdrawal by disposing the specimen(s) and/or the SDCC archives the encrypted Social Security and faxes the case report form back to the site Research Coordinator.

CONWTHDR is entered and verified in the Data Management System.

(CTECH) - Computed Tomography:

Purpose: This case report form records Computed Tomography process-related information as well as technologist and Research Coordinator contact information.

Participants assigned to the sub-cohort for Computed Tomography (**CT**)/Electron Beam Tomography (**EBT**) testing at screening visit (Visit 2) should undergo Computed Tomography/Electron Beam Tomography procedure at scheduled visits for the CRIC cohort.

Participants assigned to the Genetics study are administered Computed Tomography/Electron Beam Tomography procedure once during the course of the CRIC study.

Who: Completed by the Research Coordinator and Computed Tomography/Electron Beam Tomography technologist.

When: This case report form is completed for the CRIC cohort study at:
12-month clinic visit (Visit 5)
48-month clinic (Visit 11)

If unable to administer test at a scheduled CRIC study visit, Computed Tomography/Electron Beam Tomography can be administered at other annual clinic visits.

Computed Tomography/Electron Beam Tomography is administered on an "as needed" basis for the CRIC Genetics (ancillary) study.

Directions: This test is administered to participants assigned to Computed Tomography/Electron Beam Tomography testing in the CRIC study and to all CRIC study participants who consent to the Genetics (ancillary) study.

Computed Tomography/Electron Beam Tomography is not performed on participants over 136.2 kg (300 lbs), or with Coronary Artery Bypass Graft (CABG), coronary stenting and coronary angioplasty.

Computed Tomography/Electron Beam Tomography is also not performed on female participants who report being pregnant. The test can be administered when the condition is resolved.

Q1: Only one procedure or type of equipment must be selected, e.g. Computed Tomography/Electron Beam Tomography, GE16, GE16Pro, Siemens16, GE64, Phillip16. If the equipment is used at the site is not listed on the CRF, "Other" response must be checked and the type of equipment must be identified. Selection in this item is based on the type of equipment used at the site's Computed Tomography Center.

Q2: This is the date the procedure was performed on the participant.

Q2a: Type of Computed Tomography/Electron Beam Tomography (sub-cohort or ancillary) must be checked for appropriate disposition of the reading from the Reading Center.

The Research Coordinator should check the "CRIC (sub-cohort assignment-based)" checkbox for the participant who is selected for the CRIC Computed Tomography/Electron Beam Tomography testing and is administered Computed Tomography/Electron Beam Tomography as outlined in the visit schedule (**CHART2**).

The Research Coordinator should check the "CRIC Genetics study" checkbox for the participant who consents to participate in the Genetics (ancillary) study.

Q3: Gender selection is restricted to "Male" or "Female", as recorded on the Demographic Information (**DEMO**) at screening visit (Visit 2).

Q4: Expected response to Q4 is always "No" for female participants. Computed Tomography/Electron Beam Tomography technologist must confirm through self-report that the participant is not pregnant at the time of the procedure and must terminate the scan if the response is in the affirmative.

"N/A" must be checked in this item for male participants.

Q5: Record the most recent self-reported weight in kg or in lbs. Participants at the time of screening may be assigned to the sub-cohort if they measure at \leq 136.2 kg (300 lbs).

At the time of the Computed Tomography/Electron Beam Tomography scan a self-reported most recent weight should be <136.2 kg (300 lbs). Participants weighing in excess of 136.2 kg (300 lbs) may not be scanned because of technical difficulties.

Q6: Record a 4-digit technician ID registered in the Data Management System.

Computed Tomography/Electron Beam Tomography technologist must include contact information in the space provided that includes telephone number, pager number, etc., to allow the Reading Center to reach him/her in case of an emergency or to answer any questions related to the scan.

CRIC study Research Coordinator must complete contact information in the space provided, including telephone number and pager number and attach it to the scan sent to the Reading Center, allowing the Reading Center staff to contact the site to discuss issues or problems.

Computed Tomography Reading Center contact information is available on the case report form if the sites need to contact them.

CTECH Q1–6 only are entered and verified in the Data Management System.

(CTRANS) - Computed Tomography – Transfer:

Purpose: This is a transfer and tracking case report form faxed prior to transferring scans to the Reading Center.

Who: Completed by the Research Coordinator.

When: This case report form is completed when transferring scans to the Computed Tomography Reading Center for scans performed at 12-month clinic visit (Visit 5) and 48-month clinic visit (Visit 11) for the CRIC cohort study; [If unable to administer test at scheduled visit, Computed Tomography/Electron Beam Tomography can be administered at other annual clinic visits.]

CTRANS is completed on an “as needed” basis for the CRIC Genetics (ancillary) study.

Directions: **CTRANS** tracks batched scans from the sites to the Reading Center, with the Reading Center acknowledging the receipt of the scans by faxing it back to the sites.

The site Research Coordinator faxes this case report form when transferring the scan to the Reading Center. The Reading Center, in turn, will fax the case report form back to the site for data entry in the Data Management System.

Research Coordinator completed columns: The site Research Coordinator lists relevant information in the transfer columns, including, participant’s ID, initials, date of birth, date the test was administered to the participant, files archived locally (check “Yes” or “No”) and number of scans sent. Type of the CT/EBT scan is also identified on the transfer form to indicate a CRIC study scan or a Genetics study scan. The Reading Center cautions against exceeding the number of slices to greater than 80. The larger the number of slices, the more the participant is exposed to radioactive material.

The Research Coordinator can include comments in the appropriate column to convey information not available on the Computed Tomography (**CTECH**) case report form.

Reading Center columns: The Reading Center personnel will complete the columns to acknowledge the receipt of the scan (check “Yes” or “No”) and add comments for the Research Coordinators, noting problems or issues.

The information on the signature and date line is completed at the Computed Tomography Reading Center with the date of receipt at the Reading Center and the person acknowledging the receipt.

Computed Tomography Reading Center contact information is available if the sites need to contact them.

CTTRANS is entered and verified in the Data Management System at the site after the Reading Center acknowledges the receipt of the scan by fax.

(DEMO) - Demographic Information:

- Purpose:** This case report form collects participant demographic information and brief family history.
- Who:** Participant completed, as a self-report.
- When:** This case report form is completed at screening visit (Visit 2).
- Directions:** **DEMO** records demographic information. Ethnicity and racial background questions are linked to additional questions that explore the family origin.
- Q1: Date of birth is required to calculate eGFR in the Assignment (**ASSIGN**) module.
- Q2: Gender response in Q2 is essential to calculating eGFR in the Assignment (**ASSIGN**) module.
- If a participant has selected the option of “Other” for gender, upon review of the case report form the Research Coordinator 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.
- Q3: Check “Domestic partner” response if the participant co-habitates with a same sex or opposite sex partner in a full-time domestic relationship.
- Q4: Living with others include spouse, children, family members, significant others and room mates.
- Q7: CRIC 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, the participant is identified as “Black/African-American” for eGFR calculation.
- Q8-10: Participant checking “Other” should specify the country of origin. If applicable, more than one country may be checked.
- Q11: Participants may choose multiple responses to indicate their employment status.
- Q12: The site Research Coordinator should be available to help a participant select the most appropriate category if the participant is unsure where his/her occupation may fit in the categories provided. 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, and teacher's aide.
- Skilled labor includes certified electrician, carpenter, welder, butchers, bakers, equipment repairers, mechanics, metal workers, plant/systems operators.
- Semi-skilled labor includes construction help, mechanic's help. crane operators, drivers, parking lot attendants, sailors/deckhands.
- Unskilled labor includes porters, bell hops, manual labor, farm labor.
- Home maker.

Q14: A response of "Yes" is checked when the diagnosis of diabetes mellitus is given by a health care professional.

If the participant exhibits problems with reading and/or comprehension, the Research Coordinator may interview the participant and check the appropriate checkbox at the end to indicate that the questionnaire was interviewer-administered.

The Research Coordinator should check participant responses for completion and legibility.

DEMO data is required to determine Participant Assignment for the CRIC study and the sub-cohort.

DEMO data is entered and verified in the Data Management System as soon as possible.

(DHQ) - Diet History Questionnaire:

- Purpose:** This case report form assesses dietary factors associated with cardio-vascular disease progression in renal insufficiency.
- Who:** Participant completed, as a self-report.
- When:** This case report form is completed at:
Baseline visit (Visit 3)
24 month clinic visit (Visit 7)
48 month clinic visit (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**, should 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 is available through the CRIC study to facilitate ease and accuracy in completing the questionnaire. The audio aid guides the participant through each section of the **DHQ** with detailed instructions about estimating portion size and frequency of consumption. It also provides 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 should be written by the Research Coordinators prior to distributing or mailing the case report form 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, should be mailed (with pre-paid postage for return envelopes) to the participant ten days before the baseline visit, 24 month and 48-month clinic visits.

When the completed case report form is returned to the Research Coordinator, it should be checked for completeness and legibility of responses (blackened circles, blank responses). The Research Coordinator should 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 Research Coordinator 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 standard CRIC **DHQ**.

Important note: The Research Coordinator fills in required participant information on the first page completely prior to shipping to the SDCC for the scanning. Incomplete participant information may result in the **DHQ** being returned to the site for additional information.

Completed **DHQs** should be sent monthly by FedEx or scanned data entry forms to Marie Durborow at the SDCC:

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

(EBTSTAT) – Loss of Eligibility for EBT (CT) Testing:

Purpose: This case report form removes an assigned participant from Computed Tomography/Electron Beam Tomography testing because of permanent ineligibility or inability to undergo Computed Tomography/Electron Beam Tomography testing.

Who: Completed by the site Research Coordinator and the site Principal Investigator.

When: This case report form is completed on an “as needed” basis.

Directions: Effort must be put forth by the site personnel in maintaining the participant’s assignment at screening visit (Visit 2) to Computed Tomography/Electron Beam Tomography testing. This case report form is to be used carefully and only when the participant meets the disqualifying criteria.

EBTSTAT is completed when the CRIC study participant assigned to the Computed Tomography/Electron Beam Tomography testing after meeting eligibility criteria at the screening visit (Visit 2), either manifests conditions at the scheduled annual visit that makes him/her ineligible for Computed Tomography/Electron Beam Tomography testing permanently or the participant permanently declines Computed Tomography/Electron Beam Tomography testing.

Q1: The site Research Coordinator must check all applicable reasons to justify the participant’s permanent removal from Computed Tomography/Electron Beam Tomography testing.

Q2: By adding his/her signature and date to the case report form, the site Principal Investigator confirms the reason(s) that makes the participant permanently ineligible for Computed Tomography/Electron Beam Tomography testing. The site Principal Investigator’s signature is confirmed by checked the box under the signature line, which is then data entered in the Data Management System.

EBTSTAT is entered and verified in the Data Management System.

(ECGTRANS) - Electrocardiograph Transfer:

Purpose: This case report form records the status of CRIC study-related electrocardiograms at administration and transfer.

Who: Completed by the Research Coordinator.

When: This case report form is completed at:
 Baseline visit (Visit 3)
 12-month clinic visit (Visit 5)
 24-month clinic visit (Visit 7)
 36-month clinic visit (Visit 9)
 48-month clinic visit (Visit 11)
 60-month clinic visit (Visit 13)

Directions: **ECGTRANS** records pertinent information when performing ECGs at the sites. The completed case report form is faxed to the Central ECG Reading Center.

At the time of transmission to Wake Forest Reading Center, particular attention must be afforded to the acrostics used as identifiers by the Reading Center. Transmissions with incorrect identifiers will not be read and made invalid for analysis in the study.

Q1: Q1 cannot be left unanswered and a “Yes” or “No” response is required.

Q1a A reason must be checked if an electrocardiogram is not administered to the participant.

- Q2-4: Q2-4 must be completed if an electrocardiogram is administered to the participant.
- Q5: Cart # represents a CRIC study location to the Central ECG Reading Center. It is a numerical combination of Clinical Center number and Site number. For example, University of Pennsylvania should record 101 in this field, Tulane should record 601.
- Q6: The Research Coordinator must record “Male” or “Female” based on the gender recorded in Demographic information (**DEMO**).
- Q7: The procedure for heart square measure is described in the ECG manual in Appendix C in the Manual of Procedures.
- Heart square measure must be recorded on the case report form and cannot be left blank if an electrocardiogram is performed on the participant.
- Q8: This item records the date the electrocardiogram is electronically transferred to the Central ECG Reading Center.
- Q9: The Central ECG Reading Center will confirm the receipt of the electrocardiogram transmission to the site and the Research Coordinator should note the acknowledgement on the case report form. If the Central ECG Reading Center does not confirm the receipt of the electrocardiogram, the Research Coordinator must call to verify.

ECGTRANS data is entered and verified in the Data Management System.

(ECHOTECH) – Echocardiogram:

- Purpose:** This case report form records echocardiogram process-related information and echocardiogram technologist and Research Coordinator contact information.
- Who:** Completed by the Research Coordinator and the echocardiogram technologist.
- When:** This case report form is completed at:
12-month clinic visit (Visit 5)
48-month clinic visit (Visit 11)
Completed on an “as needed” basis for the CRIC Plus study
- Directions:** CRIC study echocardiograms, administered at scheduled annual visits, are read and the outcome is reported to the sites to be shared with the primary care physician and the participant.

Note: Participants who meet the CRIC Plus study criteria receive an additional echocardiograph at the time of eligibility to the CRIC Plus study. This echocardiogram is read by the ECHO Reading Center but the outcome is not shared with the sites in the form of a report.

This case report form records all information relevant to echocardiography.

Q1-4: These items are completed by the site Research Coordinator.

Q1-1a: This item confirms that the echocardiogram was performed.

If the test is not performed, use the appropriate checkbox(s) to explain why the test is not performed or check "Other" and briefly specify the reason.

If "No" response is checked, the rest of the case report form (Q2-8) is left blank.

Q2: This item records the date the echocardiogram was performed.

Q2a: Type of echocardiogram needs to be identified by checking the appropriate checkbox.

If the participant is scheduled for an echocardiogram based on the CRIC study visit schedule (**CHART2**), the Research Coordinator identifies the echocardiogram as "CRIC". A "CRIC" echocardiogram involves reading the scan and reporting the reading to the site.

If the participant is identified for the CRIC Plus study during a visit when an echocardiogram is not administered, the Research Coordinator identifies the echocardiogram as "CRIC Plus". A "CRIC Plus" echocardiogram is read for research purposes only and is not reported to the site.

If a participant meets the CRIC Plus study criteria at a visit where a scheduled echocardiogram is also administered, the echocardiogram is considered a CRIC study procedure and the scan is read and reported.

Q3: In this item, the Research Coordinator records height measured in cm during anthropometric testing that is recorded on the Physical Assessment (**PHYASSESS**) case report form.

Q4: In this item, the Research Coordinator record weight measured in kg during anthropometric testing that is recorded on the Physical Assessment (**PHYASSESS**) case report form.

Q5-7: These items are completed by the echocardiogram-technologist.

Q5: In this item record the participant's recumbent (lying down) systolic and diastolic pressure at the end of the test when the participant is in the supine position.

If for any reason the participant's blood pressure is not measured, check the "N/A" response.

Q6: If any of the immediate alert conditions are noted by the echocardiogram technologist or the reviewer at the site during or within 24 hours of the echocardiogram test, check the condition for the list provided and alert the appropriate CRIC study personnel listed on the case report form with the alert information.

Q7: This is a unique 4-digit ID registered in the Data Management System and identifies the echocardiogram technologist conducting the test. This information is used for Quality Assurance by the ECHO Reading Center.

Echocardiogram technologist must include contact information in the space provided that includes telephone number, pager number, etc., to allow the ECHO Reading Center to reach him/her in case of an emergency or to answer any questions from the ECHO Reading Center.

CRIC study Research Coordinator must also complete contact information in the space provided, including telephone number and pager number and attach it to the ECHOs sent to the ECHO Reading Center allowing the Reading Center staff to contact the site to discuss issues or problems.

Q8: Participants who meet the CRIC Plus study criteria and may have started hemodialysis, the date of the last hemodialysis session needs to be recorded. For all other participants "N/A" must be checked.

CRIC study Investigator must also provide his/her contact information to the ECHO Reading Center, allowing the Reading Center to report any alert results, problems or issues.

ECHOTECH Q1-8 and the type of echocardiogram (top of the page) are entered and verified in the Data Management System.

(ECHOTRANS) - Echocardiogram – Transfer:

Purpose: This case report form lists the scans sent to the ECHO Reading Center from the CRIC sites.

Who: Completed by the site Research Coordinator.

When: This case report form is completed at:
12-month clinic visit (Visit 5)
48-month clinic visit (Visit 11)

It is completed on an "as needed" basis for the CRIC Plus study.

Directions: A transfer case report form is faxed to the ECHO Reading Center prior to sending the echocardiogram test scans.

The site Research Coordinator includes this case report form in the shipment when transferring the tests to the ECHO Reading Center.

This case report form tracks batched echocardiogram tests from the sites to the ECHO Reading Center. ECHO Reading Center communicates transfer and results independently with the SDCC and the sites.

Communications from the ECHO Reading Center with sites are restricted to technical or alert-related issues based on the reviewed tests. The ECHO Reading Center also sends reports to the sites for the participant binder.

Date: Enter the date of shipment to the ECHO Reading Center.

Research Coordinator completed columns: The site Research Coordinator lists Participant IDs and Initials of the tests that are shipped to the ECHO Reading Center.

The site Research Coordinator must also indicate the type of echocardiogram that is being sent to the ECHO Reading Center.

CRIC study Research Coordinator must complete contact information in the space provided, including telephone number and pager number and include it in

the package to the ECHO Reading Center allowing the Reading Center to communicate directly with the site to discuss issues or problems.

It is not necessary to fax copies of the ECHOTRANS case report form to the SDCC.

ECHOTRANS is entered and verified in the Data Management System at the site.

(ELIG) - Eligibility Assessment:

Eligibility Assessment is one of the most important case report forms in the CRIC study. It must be completed accurately so that the participants are not erroneously included or excluded from the CRIC cohort and the sub-cohort.

Purpose: This case report form confirms a potential participant's eligibility for participation in the CRIC study and the sub-cohort.

Who: Research Coordinator or Principal Investigator completed, as an interview.

When: This case report form is completed at screening visit (Visit 2) and reviewed at baseline visit (Visit 3).

Directions: This case report form confirms the inclusion and exclusion criteria established in the protocol. Shaded responses that are checked on the case report form for specific items would exclude the participant from the CRIC study and/or the sub-cohort testing.

Most of the conditions listed in the exclusion criteria are assessed based on the self-report of the participant's past medical history. The Research Coordinators should discuss or independently review the participant's medical history if (s)he is unsure of the response.

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.

Q1-3: Since study processes cannot be administered to participants without a signed Informed Consent, Q1-3 are regulatory checks confirming that the CRIC study Informed Consent was signed and dated by the participant prior to the initiation of the screening processes.

The following are instructions to complete cohort-related exclusion items. A "Yes" response in Q4-16 excludes the participant from the CRIC study.

Q4: Reviewing the participant's response to this question (recorded in the provided space), the Research Coordinator determines if the participant is institutionalized.

Institutionalization is defined as an environment where the participant's involvement in activities outside of the institution are restricted, e.g. incarceration, long term nursing care facility, inpatient mental health facility, skilled nursing facility.

Q5: Response to cirrhosis of the liver question is based on the participant's self-report of the diagnosis.

Q6: Response to polycystic kidney question is based on the participant's self-report of the diagnosis.

- Q7: Response to this cancer of the kidney question is based on the participant's self-report of the diagnosis.
- Q8: Response to multiple myeloma question is based on the participant's self-report of the diagnosis.
- Q9: Response to HIV infection/AIDS question is based on the participant's self-report of the diagnosis.
- Q10: Response to immunosuppressive drug use question is based on the participant's self-report of use.
- Use of immunosuppressive drugs in the past 6 months excludes a participant from the CRIC study for this period of time only. Once the participant undergoes a 6 month period without use of immunosuppressive drugs, the participant may be reconsidered for screening.
- Q11: Response to dialysis question is based on the participant's self-report of the treatment.
- Dialysis for more than one month in the past excludes a participant permanently from the CRIC study.
- Q12: Response to kidney transplant question is based on the participant's self-report.
- Q13: Response to other organ or bone marrow transplant question is based on the participant's self-report.
- Q14: Response to treatment with chemotherapy question is based on the participant's self-report.
- Chemotherapy for the treatment of cancer in the past 2 years excludes a participant from the CRIC study for this period of time only. When the period of 2 years elapses, the participant may be reconsidered for screening.
- Q15: This question allows the Research Coordinator to determine if the participant is enrolled in the AASK cohort study or KEEP study.
- Note:** If a participant indicates that they are currently enrolled in a drug, device or diet study, the Research Coordinator should gather information about this from the participant and discuss the matter with the site Principal Investigator. If it appears that dual participation could have a detrimental effect on the participant, the investigator should contact the Executive Committee of the Steering Committee for review of the matter.
- Q16: This question allows the Research Coordinator 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 Executive Committee of the Steering Committee).
- Q17a-b: Response to Q17 may be checked as "Yes", but response to Q17a and Q17b must be "No" to be considered for participation in the CRIC study.

The Research Coordinator should probe to determine if the participant experiences symptoms that would diagnose NYHA Class III or IV heart failure at the screening visit (Visit 2), which excludes the participant from the CRIC study.

Q17a. Class III Heart Failure (Moderate)

NYHA Definition: Being unable to walk two level blocks or one flight of stairs without experiencing symptoms.

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

Q17b. Class IV Heart Failure (Severe)

NYHA Definition: Symptoms at rest.

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

Important Note: From reported symptoms and other health problems, it may not be clear that the participant has a clinical classification of Class III or IV heart failure. Consult with the site Principal investigator or a site physician for an appropriate classification for participants who report heart failure.

Q18. The appropriate response is checked in Q18 after reviewing responses in Q1-17. If “Yes” is checked, the participant qualifies for the CRIC cohort study with the subsequent questions determining eligibility for the CRIC sub-cohort testing.

Q18a-b: Permission for genetic testing and provision of SSN are optional processes for the cohort. 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 for research purposes.

Q18.a.1-4: If a participant indicates on the Informed Consent that (s)he agrees to providing blood specimen for any one of the genetic options available, check “Yes” for Q18a. This logic is also applied to the SPECIMEN case report form for Q4.

[This is changed from the previous version of the Manual of Procedures to accommodate processes and storage at the Central Laboratory at the University of Pennsylvania.]

Q18a1-4 are left blank if “No” response is checked in Q18a.

The participant may change his/her mind at a later date and a refusal can be re-visited by the Research Coordinator with the participant at an annual clinic visit.

Q18b: If a participant refuses to consent to the use of his/her Social Security Number for research purposes, check “No” in Q18b.

The participant may change his/her mind at a later date and a refusal can be re-visited by the Research Coordinator with the participant at an annual clinic visit.

- Q19-25: These items define the criteria that determine the participant's eligibility to participate in ¹²⁵I-iothalamate GFR testing. Participants who do not qualify for the sub-cohort are not excluded from participating in the CRIC study.
- Q19: ¹²⁵I-iothalamate GFR testing may cause an allergic reaction in participants who have iodine or shellfish allergy, making this item an exclusionary criterion.
- Q20: 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.
- Q21: 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.
- "No" is the expected response for all females of child-bearing age to qualify for ¹²⁵I-iothalamate GFR testing.
- Q21: 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.
- "No" response is an expected response for all females of child-bearing age to qualify for ¹²⁵I-iothalamate GFR testing.
- 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.
- A participant may be reconsidered for screening after the 30 day period.
- Q23-25: If a participant's response to Q23 is "Yes", the participant does not qualify for sub-cohort participation. If three (3) of the five (5) criteria listed for Q24 have a "Yes" response checked, the Research Coordinator should consult the site Principal Investigator to determine if the participant meets urinary impairment criteria.
- Q24d-e These questions are asked of males participants and "N/A" must be checked for female participants.
- Q26: A "Yes" response to this question confirms that the participant meets the eligibility criteria for ¹²⁵I-iothalamate GFR testing.
- Q27: This question allows the Research Coordinator and the Principal Investigator 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 Research Coordinator and the Principal Investigator may exclude the participant from the CRIC study.

Q27a; Space is provided for the Research Coordinators to add comments to the "Yes" response in Q27.

Q28: Participant's standing height is measured in centimeters (cm).

Q29: Participant's weight is measured in kilograms (kg). Participants weighing in excess of 136.2 kg (300 lbs) are not eligible for Computed Tomography/Electron Beam Tomography testing.

The cut-off weight of 136.2 kg (300 lbs) is determined to account for the limitations of the Computed Tomography/Electron Beam Tomography equipment.

Q29a-d: A response of "Yes" in Q29a-c renders the participant ineligible for the Computed Tomography/Electron Beam Tomography testing.

Q29d is a confirmation of the eligibility criteria in Q29, and Q29a-c for participation in Computed Tomography/Electron Beam Tomography testing.

ELIG data is entered and verified in the Data Management System as soon as possible after the screening visit (Visit 2) and prior to participant assignment.

Height and weight data measured at screening visit (Visit 2) replaces the data collected on **PHYASSESS** Q3 (height) and Q4 (weight).

Participants already in the sub-cohort, who are > 136.2 kg (>300 lbs), are not removed from the sub-cohort.

(ENCRYP) - Encryption Information:

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 Informed 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. The encryption module in the Data Management System 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.

(EVENTS) - Medical Events:

Purpose: This case report form collects participant information about medical events related to kidney and cardiac disease. It also includes other medical events that may have occurred since the last visit (annual or telephone) over the course of the CRIC study participation. Some of the information collected in this case report form is used to investigate the event(s) further to evaluate the co-morbidities with the progression of the kidney disease.

Who: Research Coordinator as an interview.

When: This case report form is completed at:
Baseline visit (Visit 3)
6-month telephone contact (Visit 4)
12-month clinic visit (Visit 5)
18-month telephone contact (Visit 6)
24-month clinic visit (Visit 7)
30-month telephone contact (Visit 8)
36-month clinic visit (Visit 9)
42-month telephone contact (Visit 10)
48-month clinic visit (Visit 11)
54-month telephone contact (Visit 12)
60-month clinic visit (Visit 13)

Directions:

The Research Coordinator completes this questionnaire as an interview with the participant. The participant is reminded of the date of the last CRIC study contact frequently to keep the participant focused on the covered time period.

If the participant is unsure if an event was previously reported at a clinic visit, the Research Coordinator should record the event information and the event would be confirmed during the ascertainment process.

This case report form is completed once only, at each phone and clinic visit. If a participant reports an event in the course of a conversation or the Research Coordinator is made aware of an event outside of a scheduled visit, the event can be noted on the **EVENTS** case report form directly or on the Comments Sheet (**COMM**) to be retrieved later when the participant is available to provide details of the event.

Q1a-c: Indicate if a doctor or a healthcare provider provided a diagnosis of heart attack [also known as myocardial infarction (MI), acute coronary syndrome (ACS) in

Q1a], stroke or mini-stroke [also known as ischemic stroke (ICH), transient ischemic attack (TIA) in Q1b] and atrial fibrillation [abnormal heart rhythm of the upper chambers of the heart (in Q1c)] since the last CRIC study contact.

Q2: The response in this item must not be left unchecked. A “Yes” or “No” response is required for event notification and event investigation.

Q2a-k: If “Yes” is checked in Q2 for hospitalization, each subsequent item requires a “Yes” or “No” response and the number of hospitalizations or ER visits per event. This information assists the Research Coordinator in event investigation.

A “Yes” response in Q2h (kidney transplant) may require completion of the Renal Replacement Therapy Primary Survey (*RRTPRIM*) or Renal Replacement Therapy Follow-up Survey (*RRTFUP*) case report forms, recording further information related to the transplant.

Information generally recorded in Q2k for other medical conditions include hospitalization for procedures and other elective surgeries for conditions not listed in Q2a-j.

Space is provided to note additional information in Q2k.

Q2l: The Research Coordinator determines number of separate hospitalizations, based on the “Yes” responses by the participant in Q2a-2k.

Note: 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 Research Coordinator should ask the participant about each test or procedure in Q3a-l. If any of the listed tests or procedures is performed, the Research Coordinator should indicate this with checking ‘Yes’ to each item and also indicate if the procedure occurred during an inpatient hospitalization or as an outpatient.

Each question requires a response and listed tests or procedures not performed are marked with a “No” response.

Data for Q3m is not collected in the CRIC study at this time.

Q4: If death is reported with a “Yes” in Q4, indicate the name and/or relationship to the participant who reported the information in the space provided.

Q4a: If death is reported, indicate the date when the participant was deceased, based on the information from the informant.

Q5a-d: Space is provided for the Research Coordinator to record the best possible information that the participant or the informant can provide to investigate reported events during event investigation at a later date.

DMS Tracking # is added in the designated space in Q5a-d when the site Research Coordinator receives event notification from the SDCC.

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

Important Note: This information initiates the next step in the event investigation process so it is imperative to collect complete and accurate information at this time. Additional information regarding the Events process is available in the EVENTS MOP Appendix I.

EVENTS data is entered and verified in the Data Management System.

The text information in Q5a-5d is not entered in the Data Management System.

(GFR) - Glomerular Filtration Rate:

Purpose: Data recorded in this case report form is used to assess kidney function by measuring clearance rate of a filtration marker from the plasma by the kidneys for participants assigned to ¹²⁵I-iothalamate GFR testing.

Who: Completed by the site Research Coordinator.

When: This case report form is completed at:
Baseline visit (Visit 3),
24 month clinic visit (Visit 7)
48 month clinic visit (Visit 11)

If the participant is unable to undergo GFR testing due to a temporary condition (not exclusionary) that is resolved at a later date, GFR testing can be performed at an unscheduled annual clinic visit.

Directions: Prior to administering the ¹²⁵I-iothalamate GFR test, the site Research Coordinator evaluates the participant for the listed safety criteria on the case report form (Pregnancy, nursing, and radionuclide test in the past 30 days) as well as other exclusion criteria listed in the protocol (iodine or shellfish allergy, self-catheterization or voiding problems). If the participant reports any conditions that are exclusionary for current or future testing, the participant is not subjected to the ¹²⁵I-iothalamate GFR test and the Research Coordinator later completes the Loss of Eligibility for ¹²⁵I-iothalamate GFR Testing (**GFRSTAT**) case report form, indicating permanent removal.

Enter the data recorded on this case report form into the electronic Data Management System as soon after the ¹²⁵I-iothalamate GFR test as possible. Data must be entered into the Data Management System by the time the samples are received at the GFR Central Laboratory because the information stored in the database is essential to the GFR Central Laboratory for calculating and reporting ¹²⁵I-iothalamate GFR test values in the Data Management System.

One (1) baseline and two (2) clinic visit ¹²⁵I-iothalamate GFR tests are administered to the participant based on the CRIC study visit schedules, but may be deferred to non-scheduled annual clinic visits only if the participant is unable to undergo testing for safety reasons at the current visit and is able to be tested once the condition(s) is resolved.

¹²⁵I-iothalamate GFR testing at a scheduled clinic visit is deferred on a female participant who is pregnant or nursing until after these conditions are resolved.

A photo copy of this case report form must be included with the GFR specimens in the packing crate.

Refer to the GFR Manual in Appendix D of the Manual of Procedures for administering the ^{125}I -iothalamate GFR test to the participant.

Q1: The date the ^{125}I -iothalamate GFR test is administered is recorded in this item.

Q2: This information is not recorded in the CRIC study at this time.

Q3: The most recent participant measured weight is recorded in kg. On rare occasions, in the absence of a measured weight, self-reported weight may be recorded.

Q4-5: This information is not recorded in the CRIC study at this time.

Q6-7: 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 the ^{125}I -iothalamate GFR test date.

The expected response in Q7 for the pregnancy test on a female participant of child-bearing age is "Negative". A positive pregnancy test excludes a participant from ^{125}I -iothalamate GFR testing at baseline and deferred at a scheduled annual clinic visit until the pregnancy is resolved.

Q8: 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.

Q9-9a: If NSAIDs or aspirin is taken within 48 hours of ^{125}I -iothalamate GFR test and are not part of a daily prescribed regimen, the test is rescheduled for 48 hours after the last use.

Q12a-d: If the discard urine volume is less than 250 ml, hydration must be continued, with a wait period of another 30 minutes. The new time is reported in Q12a and the new volume is reported in Q12b.

Q13-16: Information cannot be missing and must be recorded for each item in Q13a-d, Q14a-d, Q15a-d and Q16a-d. Data is essential for ^{125}I -iothalamate GFR calculation and is also used for Quality Assurance at the GFR Central Laboratory.

Q17a-d: A fifth (5th) period is added when problems occur with voiding or specimen collection during any of the preceding 4 periods.

Q18: Space is provided to record any problems encountered during testing that may be of relevance to the GFR Central Laboratory in determining the validity of the test.

Tech ID: This is a 4-digit technician ID registered in the Data Management System.

GFR data is entered and verified in the Data Management System within 24 hours of the test.

(GFRSTAT) – Loss of Eligibility for ¹²⁵I-Iothalamate GFR testing:

- Purpose:** To remove an assigned participant from ¹²⁵I-lothalamate GFR testing because of permanent ineligibility or inability to undergo ¹²⁵I-lothalamate GFR testing.
- Who:** Completed by the site Research Coordinator and the site Principal Investigator.
- When:** This case report form is completed on an “as needed” basis.
- Directions:** Effort must be put forth by the site personnel in maintaining the participant’s assignment at screening visit (Visit 2) to ¹²⁵I-lothalamate GFR testing. This case report form is to be used only when the participant meets the disqualifying criteria.

GFRSTAT is completed when the CRIC study participant, assigned to the 125I-lothalamate GFR testing after meeting eligibility criteria at the screening visit (Visit 2), either manifests conditions at the scheduled annual visits that would make him/her ineligible for 125I-lothalamate GFR testing permanently or permanently declines 125I-lothalamate GFR testing.

- Q1: The site Research Coordinator must check as many reasons applicable to justify the participant’s permanent removal from the ¹²⁵I-lothalamate GFR assignment.
- Q2: By adding his/her signature and date to the case report form, the site Principal Investigator confirms the reason(s) that makes the participant permanently ineligible for ¹²⁵I-lothalamate GFR testing. The site Principal Investigator’s signature is confirmed by checking the box under the signature line, which is then data entered in the Data Management System.

GFRSTAT is entered and verified in the Data Management System.

(GFRTRANS) - GFR - Specimen Transfer:

- Purpose:** This case report form records specimen status for collection and transfer for ¹²⁵I-lothalamate GFR testing.
- Who:** Completed by:
Research Coordinator at the site
GFR Central Laboratory personnel;
University of Pennsylvania Central Laboratory personnel
- When:** This case report form is completed at:
Baseline visit (Visit 3)
24-month clinic visit (Visit 7)
48-month clinic visit (Visit 11)
- Directions:** Refer to Appendix D of the Manual of Procedures for GFR testing.

The Research Coordinator records the information on specimen availability, shipping information and Research Coordinator contact information for the GFR Central Laboratory and the Central Laboratory at the University of Pennsylvania.

The GFR Central Laboratory personnel and the Central Laboratory personnel at the University of Pennsylvania complete the information in relation to the receipt and condition of the specimen and fax the case report form back to the site.

Q1-2: Data is not collected for these 2 items in the CRIC study at this time.

Q3: 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.

Each specimen must be accounted for availability and shipment and cannot be left blank.

Q4: Specimen status for Central Laboratory at the University of Pennsylvania 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.

Each specimen must be accounted for availability and shipment and cannot be left blank.

The specimens are shipped to the GFR Central Laboratory and Central Laboratory at the University of Pennsylvania. Personnel at each Central Laboratory determine whether the specimen is received, and if received, whether the specimen is in an acceptable condition.

Prior to shipping, the Research Coordinator advises Central Laboratory personnel of the shipment of specimens to be received the following day, by faxing the **GFRTRANS** case report form. This helps the Central Laboratory personnel anticipate the shipment and also notify the Research Coordinator if the shipment is not received as scheduled. When the shipment is received, and the condition of the specimens determined, the Central Laboratory personnel faxes the completed case report form to the Research Coordinator for data entry and verification.

If specimens are sent on different days, the Research Coordinator should record information on separate case report forms, indicating a different shipping date for each shipment. A copy of the completed **GFRTRANS** case report form should be sent with each shipment.

When the completed **GFRTRANS** is received at the site, the Research Coordinator enters and verifies the data in the Data Management System. If necessary, multiple entries of the case report form with unique visit dates may be entered.

(KCQ) - The Kansas City Questionnaire:

Purpose: The items in this questionnaire assess the participant's quality of life and the symptoms related to cardiomyopathy (shortness of breath, fatigue, ankle swelling, etc.).

Who: Participant completed, as a self-report

When: This case report form is completed at:
12-month clinic visit (Visit 5)
24-month clinic visit (Visit 7)

36-month clinic visit (Visit 9)
48-month clinic visit (Visit 11)
60-month clinic visit (Visit 13)

Directions: **KCQ** is completed as a self-report. The participant should be instructed to read the instructions carefully.

The participant is instructed to check one response per item, and to also note that the activities are time-limited (2 weeks).

The Research Coordinator checks responses for completion and legibility.

If the questionnaire is completed with significant assistance from the interviewer, the Research Coordinator should check the appropriate box at the end of the questionnaire.

If the interviewer administers this questionnaire to the participant at baseline visit (Visit 3) because of reading or comprehension issues, the interviewer must administer the interview to the participant at all subsequent visits to maintain consistency in administration.

KCQ data is entered and verified in the Data Management System.

(KDQOL) - Kidney Disease and Quality of Life Questionnaire:

Purpose: The items in this questionnaire assess the participant's quality of life and rate kidney-specific health issues.

Who: Participant completed, as a self-report.

When: This case report form is completed at:
Baseline visit (Visit 3),
12-month clinic visit (Visit 5)
24-month clinic visit (Visit 7)
36-month clinic visit (Visit 9)
48-month clinic visit (Visit 11)
60-month clinic visit (Visit 13)

Directions: **KDQOL** is completed as 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 Research Coordinator should check responses for completion and legibility.

If the questionnaire is completed with significant assistance from the interviewer, the Research Coordinator should check the appropriate box at the end of the questionnaire.

If the interviewer administers this questionnaire to the participant at the baseline visit (Visit 3) because of reading or comprehension issues, the interviewer must administer the interview to the participant at all subsequent visits to maintain consistency in administration.

KDQOL data is entered and verified in the Data Management System.

(LABCBC) - Laboratory Results – CBC:

Purpose: Complete Blood Count (CBC) results, based on site-specific (local) laboratory report are recorded on this case report form.

Who: Completed by the Research Coordinator.

When: This case report form is completed at:
 Baseline visit (Visit 3)
 12-month clinic visit (Visit 5)
 24-month clinic visit (Visit 7)
 36-month clinic visit (Visit 9)
 48-month clinic visit (Visit 11)
 60-month clinic visit (Visit 13)

Directions: CBC results are obtained from blood drawn and sent to the site-specific (local) laboratory. The Research Coordinator should transfer results from the laboratory-generated report to **LABCBC**.

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

Any copies sent to the SDCC at their request must have the participant's personal information obliterated and the copy identified by Participant ID, Participant Initials and Visit Number only. The original copies must maintain participant's personal identifiers.

LABCBC data is entered and verified in the Data Management System.

(MEDHX) - Medical History:

Purpose: This case report form collects relevant participant medical history in areas of general health, renal and cardiovascular health, diabetic status, social history and brief family history.

Who: Participant, as a self-report, or where participant has problems with reading or comprehension, interviewer administered.

When: This case report form is completed at baseline visit (Visit 3).

Directions: Instructions for completing the questionnaire should 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.

Several items have "skip patterns", where certain sections are bypassed if the leading question has a response of "No", indicating that the participant is not diagnosed for the listed condition. These skip patterns need to be followed to maintain consistency in responses. The Research Coordinator must clarify any discrepancies in responses observed during review of the questionnaire with the participant prior to the end of the CRIC study visit.

Data from this questionnaire is critical during data analysis for categorizing participants based on their medical history and is validated at the SDCC to maintain consistency in responses.

Q2-11: These items are relevant to female participants and male participants must “skip” to the next section.

Q15: If the response is ‘No,’ the participant should not complete the three (3) sub-questions.

Q18a-c: If the response is “Yes” for any of the sub questions, a Medical Events (**EVENTS**) case report form may need to be completed.

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

The Research Coordinator should check responses for completion and legibility. Special attention should be given to skip pattern responses during the review process.

If the Research Coordinator’s review of the participant’s CMED data indicates that the participant is prescribed medications for the conditions listed in CMED, the Research Coordinator can revise the participant’s “No” response to a “Yes” response. A note can be added on the comment sheet to explain the reason for a change.

If the questionnaire is completed with significant assistance from the interviewer, the Research Coordinator should check the appropriate box at the end of the questionnaire.

If the interviewer administers this questionnaire to the participant at the baseline visit (Visit 3) because of reading or comprehension issues, the interviewer must administer the clinic visit version of the interview (**MEDHXUP**) to the participant at all subsequent visits to maintain consistency in administration.

MEDHX data is entered and verified in the Data Management System.

(MEDHXUP) - Medical History Update:

Purpose: This case report form is an abbreviated version of the Medical History questionnaire used at the baseline visit. It is administered as a self-report to the participants at annual clinic visit clinic visits and updates medical history information on new diagnoses and new treatments since the last clinic visit. Prior (prior to this visit and captured at an earlier visit) diagnosis and treatment response options are also added to distinguish between newly-mentioned and earlier diagnoses and treatments.

Who: Participant, as a self-report, or where participant has problems with reading or comprehension, interviewer administered.

When: This case report form is completed at:
 12-month clinic visit (Visit 5)
 24-month clinic visit (Visit 7)
 36-month clinic visit (Visit 9)
 48-month clinic visit (Visit 11)
 60-month clinic visit (Visit 13)

Directions: Instructions for completing the questionnaire must be reviewed with the participant. Prior to attempting to respond to the questions, the site Research Coordinator must orient the participant to the time period covered when referenced to “Since the last clinic Visit...” to accurately capture new medical information. This time period can be obtained from the

previous visit information. Space is provided at the start of the questionnaire for the Research Coordinator to fill in the information in preparation for the visit.

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/her best judgment or estimate and respond. Responses to questions must not remain blank, except for relational questions. For relational questions, certain types of responses have instructions for the skip patterns that the participant must be instructed to follow.

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

Throughout the questionnaire, a “Yes” response is generally restricted to new treatments or diagnoses. If a condition is previously diagnosed and the participant receives on-going treatment, an “On-going treatment for a pre-existing diagnosis” response category is added where applicable.

The Research Coordinator should check responses for completion and legibility. Special attention should be given to skip pattern responses when checking.

If the questionnaire is completed with significant assistance from the interviewer, the Research Coordinator should check the appropriate box at the end of the questionnaire.

If the interviewer administers this questionnaire to the participant at an annual clinic visit because of reading or comprehension issues, the interviewer must administer the interview to the participant at all subsequent visits to maintain consistency in administration.

MEDHXUP data is entered and verified in the Data Management System.

(MISSVST) – Missed Visit Information:

Purpose: This case report form is used to record a missed annual clinic visit for a participant after an extended window closes and the next visit window opens to account for missing data at an annual clinic visit.

Who: Completed by the Research Coordinator.

When: This case report form is completed on an “as needed” basis when the participant fails to keep a scheduled annual clinic visit.

Directions: Attempts to engage the participant in the annual clinic visit process within the generous time frame of two (2) months before and two (2) months after the follow-up target date must be a top priority at the site.

With the annual clinic visit window in the CRIC study extended until the time when the next annual clinic visit window opens (12 month period), this case report form is completed only when an extended window closes and the next annual clinic visit window opens.

Check appropriate checkboxes to best represent the reason(s) for the participant missing an annual clinic visit. Multiple reasons may be checked.

MISSVST data is entered and verified in the Data Management System.

(MMSE) - Modified Mini-Mental State Exam:

Purpose: This test administered to the participant assesses the participant's cognitive function status.

Who: Administered and completed by the Research Coordinator.

When: This test is administered at:
Baseline visit (Visit 3)
24-month clinic visit (Visit 7)
48-month clinic visit (Visit 11)

Directions: Refer to the MMSE Manual in Appendix E of the Manual of Procedures for administering MMSE to the participant. Visual Aids have been distributed to the Research Coordinators.

Data from Q18 and higher of the case report form and the total scores per item are entered and verified in the Data Management System.

(NSPEC) - Nail Specimen:

Purpose: This case report form records acquisition of nail specimens.

Who: Completed by the Research Coordinator.

When: This case report form is completed at:
Baseline visit (Visit 3)
12-month clinic visit (Visit 5)
24-month clinic visit (Visit 7)
36-month clinic visit (Visit 9)
48-month clinic visit (Visit 11)
60-month clinic visit (Visit 13)

Directions: Refer to Nail Clipping Procedure in Appendix A of the Manual of Procedures.

Complete Q1 of this case report form even if nail specimens were not acquired and indicate the reason in Q1a.

Fingernail clippings are preferred over toenail clippings.

NSPEC is entered and verified in the Data Management System.

(OFFSTVST) – Off-Site Visit Information:

Purpose: This questionnaire collects pertinent information on the annual clinic visit that is conducted at an off-site location.

Who: Completed by the Research Coordinator starting with Visit #7.

When: This case report form is completed on an "as needed" basis when the participant cannot keep a scheduled annual clinic visit and an off-site visit is possible to complete the visit-specific assessment.

Directions: If a study participant is unable to make a scheduled annual visit to the clinical site, the Research Coordinator or designee can arrange with the participant to be seen at a location convenient to both. Please refer to the off-site visit manual in Appendix### for further information.

An off-site visit can only be initiated at Visit 7. This case report form is completed when the Research Coordinator returns from the off-site visit. A generic list of processes and assessments (relevant to study data collection) is listed on the case report form, as well as the reasons for and location of the off-site visit.

Q1: This question collects administrative information related to the visit number and the visit date. Q 1c confirms if the regulatory process of re-consenting, if necessary, is followed.

Q2a-z: Any process or assessment completed at this visit is indicated by checking the appropriate box. These are divided into 4 categories to facilitate preparation for the off-site visit. Administrative case report forms for the visit are not listed here and its need and use is left to the discretion of the Research Coordinator or designee.

Q3: A list of reasons with checkboxes is provided to indicate all applicable reasons for conducting the annual visit off-site. "Other" option is used if the reason does not fit into the responses that are provided.

Q4: A list of likely locations is provided and only one response is required. "Other location" option is used if the visit was conducted at a location not listed.

OFFSTVST data is entered and verified in the Data Management System.

(PHYACT) - Physical Activity:

Purpose: This questionnaire is an assessment of the participant's physical activity.

Who: Participant completed, as a self-report.

When: This case report form is completed at:
Baseline visit (Visit 3)
24-month clinic visit (Visit 7)
48-month clinic visit (Visit 11)

Directions: The completion instructions should be reviewed with the participant.

The Research Coordinator should check responses for completion and legibility. Special attention should be given to skip pattern responses when checking.

If the questionnaire is completed with significant assistance from the interviewer, the Research Coordinator should check the appropriate box at the end of the questionnaire.

If the interviewer administers this questionnaire to the participant at the baseline visit (Visit 3) because of reading or comprehension issues, the interviewer must administer the interview to the participant at subsequent visits to maintain consistency in administration.

PHYACT data is entered and verified in the Data Management System.

(PHYASSESS) - Physical Assessment:

Purpose: This case report form records anthropometric measures, Ankle Brachial Index (ABI), and Bioelectric Impedance Assessment (BIA) data for the CRIC cohort and CRIC Plus study participants.

Who: Completed by the site Research Coordinator or a designee.

When: With the introduction of CRIC Plus study, Anthropometry, Ankle Brachial Index (ABI) and Bioelectric Impedance (BIA) are measured at each annual clinic visit:
 Baseline visit (Visit 3)
 12-month clinic visit (Visit 5)
 24-month clinic visit (Visit 7)
 36-month clinic visit (Visit 9)
 48-month clinic visit (Visit 11)
 60-month clinic visit (Visit 13)

Directions: Refer to the Physical Measures section in Appendix A of the Manual of Procedures for anthropometric measurements, ABI and BIA procedures.

Check the "Not measured" box to explain missing data where applicable if the participant is an amputee and physical measures cannot be recorded.

Q1-2: Record date and time of the physical measures administered to the participant.

Anthropometric measures are recorded in Q3-5.

Q3-5: Height is measured and recorded in cm;
 Weight is measured and recorded in kg;
 Waist circumference is measured and recorded to the nearest cm.

Ankle Brachial Index (ABI) measures are recorded in Q5-13.

If it is not possible to measure all six (6) blood pressures because of surgery, amputation, illness or other conditions, one measure on each leg is recorded and an explanation is made available in source documentation for recording fewer measures. At least one reading on each side is needed to calculate the ABI ratio.

Q6 11: Measure and record blood pressure (systolic blood pressure only) on the 3 locations identified on the right side of the body.

Repeat the same measures on the left side of the body.

If the systolic pressure in items 6-11 is 300 mmHg or higher, a value of 300 is recorded on the CRFs. If the systolic pressure is not readable, the item must be left blank on the CRF. A value should not be entered in the DMS to indicate missing data. An explanation sent by the site to the SDCC to a query will be a confirmation of the missing data.

Q12-13: Ankle Brachial Index is calculated internally by the Data Management System and the calculation is not available to the sites.

If the Research Coordinator needs to manually calculate ABI to share the results with the participant or his/her primary care physician, the equation for the ratio is provided below and is also available for reference on the case report form:

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.

Bioelectric Impedance Assessment is recorded in Q14-17 and 19.

Q14: Record the body position during the test. The position selected at the baseline visit (Visit 3) is repeated at subsequent clinic visits.

Q15: Record the side used for the test. The side selected at the baseline visit (Visit 3) is repeated at subsequent clinic visits.

Q16-17: Record readings from the BIA equipment.

Q19: An implanted defibrillator excludes the participant from Bioelectric Impedance Assessment (**BIA**). Indicate by checking the appropriate box if the participant has an implanted defibrillator. In case of an implanted defibrillator, data in Q14-17 should remain missing.

Q18: 2 items should be completed – whether one or multiple technicians administered the tests and identify the technician(s) by recording Tech IDs.

The Research Coordinator indicates whether one (1), or more than one (1) technician performed the tests.

If one (1) technician performed the test, the box coded “1” should be checked and technician ID that is registered in the Data Management System should be recorded.

If more than one (1) technician performed the test, the box coded “2” should be checked and the technician ID for each of the 3 tests should be recorded individually, even though the technician ID is repeated.

Except in situations where 1 person performs the test and the ID is recorded only once, data in Q18 cannot be left missing.

This data is used in monitoring Quality Assurance in the CRIC study processes.

PHYASSESS data is entered and verified in the Data Management System.

(PREREF) - Prescreening Refusal:

Purpose: This case report form records information leading to the termination of a potential participant who meets the CRIC study criteria, but refuses CRIC study participation.

Who: Completed by the Research Coordinator.

When: This case report form is completed at prescreening contact (Visit 1) only and the reasons for refusal are specific to the prescreening contact.

Directions: The outcome of the prescreening contact should help the Research Coordinator and the Principal Investigator 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 Research Coordinator should terminate the participant at the prescreening contact (Visit 1).

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

Brief comments should be noted in the space provided for “Other” reasons.

Participant ID assigned to a participant who refuses the CRIC study cannot be re-used.

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

(PRESCR) - Prescreening Information:

Purpose: This case report form facilitates prescreening of a potential participant to determine general CRIC study eligibility based on broad inclusion/exclusion CRIC study criteria.

Who: Completed by the Research Coordinator or designee.

When: This case report form is completed at prescreening contact (Visit 1) only and involves direct contact with the participant, either by phone or in-person.

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

Q1: A site-specific script (**SCRIPT1**), briefly explaining the CRIC study, is developed to facilitate the prescreening process.

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

(b) Verbal consent must also be obtained from the potential participant during an 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.

Q2-5: These questions confirm the essential demographic information that may also be available on the Health Data Review (**HDREV**) case report form.

Q6: Diagnosis of diabetes mellitus should be given by a healthcare provider.

“Yes” responses in Q7-11 would generally deem the participant ineligible for participation. A “Don’t know” response should be checked further through available medical history or medical records. Information provided by the participant that may be unclear should be discussed with the site’s Principal

Investigator for final determination, prior to scheduling the participant for the screening visit (Visit 2).

- Q7: Noting the participant's response to this question, the Research Coordinator determines if the participant is institutionalized.

Institutionalization is defined as an environment where the participant's involvement in activities outside of the institution are restricted, e.g. incarceration, long term nursing care facility, inpatient mental health facility, skilled nursing facility.

If institutionalized, the participant is considered ineligible for participation.

- Q8a-g: Refer to the inclusion/exclusion criteria script, Exclusion Script (**SCRIPT2**), developed for the Research Coordinators to discuss exclusion criteria with potential participants.
- Q9a: Refer to the list of immunosuppressive drugs below generally prescribed in renal disease that would make the participant ineligible.

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	Celcept
Antineoplastic Agent	Chlorambucil	Leukeran
Adrenocorticosteroid	Prednisone	

- Q9b-d: Refer to the inclusion/exclusion criteria script - **SCRIPT2**, developed to discuss exclusion criteria with potential participants.
- Q10: This question allows the Research Coordinator to probe for other serious medical conditions that may prevent or may exclude the participant from being considered for the CRIC study.
- Space is provided to record this information for discussion with the Principal Investigator, if necessary.
- Q11: This question allows the Research Coordinator and/or the Principal Investigator to determine if the participant is enrolled in another trial. Depending on the type of trial (s)he is enrolled in, the Research Coordinator and/or the Principal Investigator 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 Principal Investigator.

Q12: The Research Coordinator should discuss participant responses in Q7-11 that are questionable with the CRIC study Principal Investigator to determine eligibility.

If the participant apparently seems qualified for participation – “Not ineligible”, s(he) should be scheduled for a screening visit (Visit 2).

If the participant answers “Yes” to any of the prescreening criteria, the participant does not qualify (“Ineligible”) for the CRIC study, and the Research Coordinator should end the contact.

Q12a: If the participant seems qualified based on prescreening responses but refuses participation, the Research Coordinator should complete Prescreening Refusal (**PREREF**) case report form.

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

The Research Coordinator 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** is entered in the prescreening module in the Data Management System. See the Data Management System User Guide in this manual for more information.

Note: All Participants must have a Prescreening Information (**PRESCR**) case report form. The entire case report form must be completed in writing. The following procedures minimize the data entry process:

- **PRESCR** case report form is single entry ONLY.
- This case report form must be entered into the Data Management System on or before the screening visit (Visit 2).
- If a participant refuses prescreening, enter Q1 only in the Data Management System.
- If a participant agrees to the prescreening contact and is eligible at this point, enter Q1-6 and Q12 in the Data Management System and additional data may not be entered.
- If a participant is ineligible, enter Q7-12, to record responses that excluded them.

(PROXY) - PROXY Information:

Purpose: This case report form facilitates data collection on behalf of the participant when the participant is unable to provide the information due to death or illness.

Who: Completed by the Research Coordinator.

- When:** This case report form is completed at any study visit where the participant is unable to provide study related information.
- Directions:** Since proxy data is not a substitute for actual data collection, all effort should be made to talk directly to the participant. If direct participant contact is determined to be impossible, proxy data should be considered to collect, at a minimum, partial study information. Due to illness (or death) if the participant is unable to be interviewed, a family member, friend, caregiver or any person who has intimate knowledge of the participant and his/her health can provide the information on behalf of the participant. Collection of proxy data is limited to concomitant medication (CMED), medical events (EVENTS), updates to previously provided medical history (MEDHXUP), and renal replacement therapy information (RRT case report forms).
- Q1: Administrative information related to the visit number and date is collected on Q1.
- Q2: Proxy data is identified by checking the appropriate box(s) linked to all the applicable case report form.
- Q 3: Applicable reasons are indicated for the proxy session in Q3.
- Q4: This question identifies the relationship of the person who was contacted for proxy data. One response is accepted for this question. "Other" response is checked when none of the available responses apply.

PROXY data is entered and verified in the Data Management System.

(PROTRANS) - Proteomics Specimen Transfer:

- Purpose:** This case report form records Proteomics specimen status during collection at the site and transfer to the Central Laboratory.
- Who:** Completed by the Research Coordinator.
- When:** This case report form is completed at:
Baseline visit (Visit 3)
12-month clinic visit (Visit 5)
24-month clinic visit (Visit 7)
36-month clinic visit (Visit 9)
48-month clinic visit (Visit 11)
60-month clinic visit (Visit 13)
- Directions:** Additional information is available in the Proteomics protocol in Appendix J of this Manual of Procedures.
- A 90 ml clean catch urine specimen is collected from participants at the baseline visit (Visit 3) and each annual clinic visit thereafter.
- Urine specimens may be collected over 2 time periods on a given day for a visit and processed as combined specimen if the participant experiences problems voiding the amount required.
- Proteomics specimen should be collected prior to GFR testing.
- PROTRANS** is entered and verified in the Data Management System.

(PTCL) - Participant Close-out:

Purpose: By completing this case report form the site Research Coordinator and the site Principal Investigator confirm that the data collected on the CRIC study participant are correct, according to the CRIC study protocol and to the best of the Principal Investigator's and Research Coordinator's knowledge.

Who: Site Principal Investigator and site Research Coordinator completed.

When: This case report form is completed at:
60 month clinic visit (Visit 13) or at premature termination.

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

If this case report form is completed between scheduled visits, the Research Coordinator should record the next visit number and the current date in the header.

PTCL is entered and verified in the Data Management System.

(PUP) - Procedural or Unanticipated Problems:

Purpose: This case report form is used to record reportable problems associated with a CRIC study testing procedure(s).

Who: Completed by the site Research Coordinator and the Principal Investigator.

When: This case report form is completed on an "as needed basis" when a participant reports problems during or after administration of a CRIC study medical/research procedure.

Directions: *PUP* must be completed and data-entered within 72 hours of the first report of CRIC study-related problems, e.g. during blood draw for laboratory testing, ¹²⁵I-iothalamate GFR testing-related problems.

The Research Coordinator must share this information with the CRIC study Principal Investigator and CRIC 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 generates *PUP* reports for the Sponsor, NIDDK, at predetermined intervals.

The case report form allows 2 reports to be recorded per page. If more than 2 incidents at a specified visit occur, additional pages are available to record multiple reports.

Reports are visit-specific. The Research Coordinator should record the visit date associated with the problematic procedure in the case report form header, regardless of when the site is first notified of the incident.

Alpha-numeric *PUP* codes have been provided on the case report form 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 processes.

There are no known procedural problems associated with Ankle Brachial Index (ABI), 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” case report form, the expected response for Q1 should always be “Yes”.

The “Yes” response triggers 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 listed on the case report form for easy reference.

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 Research Coordinator 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 Procedural or Unanticipated Problems - Additional Page (**PUPADD**), available within the “Forms” module of the Data Management System.

PUP data is entered and verified in the Data Management System. In addition to data entry in the Data Management System, this case report form should be faxed to the SDCC. This will permit prompt evaluation of participant data.

The Clinical Management Committee also evaluates the information contained on the **PUP** forms

(RRTPRIM) - Renal Replacement Therapy – Primary Survey:

Purpose: This case report form collects additional information on End Stage Renal Disease (ESRD) if Q2h and/or Q3l are checked as “Yes” for the first time on the Medical Events Questionnaire (**EVENTS**).

Who: Completed by the Research Coordinator.

When: This case report form is completed the first time that the participant responds “Yes” to Q2h and/or Q3l on the **EVENTS** case report form.

At subsequent contacts (clinic or phone) the Renal Replacement Therapy – Follow-Up Survey (**RRTFUP**) should be used to collect clinic visit information on dialysis and/or transplant.

Directions: The first time that the participant responds positively to the dialysis or renal transplant questions on the **EVENTS** case report form, the Research Coordinator should further query the participant using the **RRTPRIM** case report form.

Q1-12: Skip pattern instructions lead the Research Coordinator through the current and past dialysis and related questions.

Q13-18: These items record kidney transplant information.

RRTPRIM is entered and verified in the Data Management System.

(RRTFUP) - Renal Replacement Therapy – Follow-Up Survey:

Purpose: To update information on the progression of End Stage Renal Disease (ESRD) at subsequent contacts (clinic or phone) after the participant first reports start of dialysis and/or kidney transplant on Medical Events Questionnaire (**EVENTS**) and consequently on the Renal Replacement Therapy – Primary Survey (**RRTPRIM**).

Who: Completed by the Research Coordinator.

When: This case report form is completed at subsequent contacts (clinic and phone) after the first response of “Yes” to Q2h and/or Q3l on the **EVENTS** case report form and at each annual visit after the RRTPRIM case report form is completed.

Directions: This case report form is completed as an update at each contact (clinic or phone) after the participant first reports renal problems on **EVENTS** and provides subsequent information.

Q1-5: These items refer to the participant’s dialysis status.

Q6-7: These items refer to the participant’s kidney transplant status.

Skip patterns guide the Research Coordinator through dialysis and kidney transplant questions.

RRTFUP is entered and verified in the Data Management System.

(SCRLAB) - Screening Laboratory Results:

Purpose: This case report form is used to record local laboratory test results to determine participant eligibility at screening visit (Visit 2).

Who: Completed by the Research Coordinator.

When: This case report form is completed at screening visit (Visit 2).

Directions: Local laboratory results are recorded on this case report form. CRIC study eligibility is determined by the serum creatinine value measured at this visit.

Q1-2: The date and time of the blood draw are recorded in these items.

Q3: Use the following Institution Laboratory Code to identify the testing laboratories:

CC ID	LAB CODE	Laboratory Name	Location
01	101	Pepper Laboratory, U of PA	Philadelphia, PA
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	301	GFR Central Laboratory at the Cleveland Clinic Foundation	Cleveland, OH
03	302	University Hospitals of Cleveland	Cleveland, OH

CC ID	LAB CODE	Laboratory Name	Location
03	303	The Cleveland Clinic Foundation	Cleveland, OH
03	304	MetroHealth Medical Center	Cleveland, OH
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
04	404	VA Hospital Ann Arbor	Ann Arbor, MI
05	501	UIC Clinical Pathology Laboratories	Chicago, IL
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

Q4: A response is recorded to identify non-fasting blood specimen.

Q5: This specimen is sent to the Central Laboratory at the 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.

Q6-7: Site-based laboratory results are recorded for serum creatinine and serum glucose. The Research Coordinator records values as they are available on the laboratory report source document.

A correction factor is applied to the serum creatinine results because of variance in local testing as compared to the Central Laboratory at the University of Pennsylvania. The corrected value for serum creatinine is available on the screen at the time of data entry and can be noted on the case report form next to site-based results.

Q9a-c: Follow directions from the dipstick manufacturer to determine if the result is positive or negative.

Q10: "Not Done" should be checked for males or post-menopausal females.

Source documentation must be available to confirm female participant's post-menopausal status.

Any copies sent to the SDCC at their request must have participant's personal information obliterated and the copy identified by Participant ID, Participant Initials and Visit Number only. The original copies must maintain participant's personal identifiers.

SCRLAB data is entered and verified in the Data Management System.

(SPECIMEN) - Specimen Collection:

Purpose: This case report form is used to record blood/serum and urine specimen status at the time of collection and during shipment.

Who: Completed by the Research Coordinator and Central Laboratory personnel.

When: This case report form is completed at:
Baseline visit (Visit 3)
12-month clinic visit (Visit 5)
24-month clinic visit (Visit 7)
36-month clinic visit (Visit 9)
48-month clinic visit (Visit 11)
60-month clinic visit (Visit 13)

Directions: Refer to Laboratory Procedure Manual in Appendix B of the Manual of Procedures.

Information on this case report form assists the Central Laboratory personnel in noting the date and time of the collection and the condition of the blood and urine specimens. This data also helps determine whether the specimens shipped are utilizable for laboratory analysis.

SPECIMEN is a “single” case report form that 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 or the blood is drawn over multiple sessions of a visit at the participant’s request. The case report form can be completed again at the site with a new date.

Q1: This item identifies the type of specimen that is shipped to the Central Laboratory.

Q2: Date of birth assists the Central Laboratory personnel determine normal ranges, if age is applicable.

Q2a: 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.

Q3: A diagnosis of diabetes mellitus, given by a healthcare provider, prompts the Research Coordinator to collect and the Central Laboratory personnel to expect Specimen #7 – 5 ml purple top tube –for HbA1C analysis.

Q3a. This question refers to the participant’s enrollment in the CRIC Plus study based on the qualifying list generated by the SDCC. The “Yes” box is checked if the participant is enrolled and actively participates in CRIC Plus processes.

Q4: “Did the participant agree to genetic testing?” If the participant answered “No” to all four of the genetic testing questions (Q18 a1-4) on the Eligibility Assessment (**ELIG**) case report form, check the “No” box. If the participant has checked “Yes” to any one of the four genetic testing questions on the **ELIG** case report form, check the “Yes” box.

Q5-6: This item records the blood draw information and identifies fasting blood specimen for Central Laboratory personnel.

Note: Specimen #7 is collected for all participants at the baseline visit. However, at annual clinic visits, this specimen is collected on diabetic participants only.

Q7-8: These items record collection information on the 24-hour urine specimen. 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 time for specimen collection is considered acceptable if collected between 22 to 26 hours.

Q9: The minimum acceptable volume for a 24-hour urine specimen is considered to be 500 ml. Volume less than 500 ml may be rejected by the Central Laboratory and another specimen collection may be requested.

Q10 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**) case report forms. Nail specimen and Serum Creatinine Specimen have also been assigned numbers for tracking purposes in the Data Management System.

Spec. #7: Purple top - 5 ml tube is collected at the baseline visit for all participants and for diabetic participants only during clinic visit visits. At clinic visit visits, check “No” for specimen collection, and “Not required” as reason for participants who are not diabetic.

Each specimen in the grid, identified by a number, cannot be left blank and must be accounted for by checking a response of “Yes” or “No” for single or multiple entries of the case report form.

This case report form is completed by the Research Coordinator and a copy is included in the shipping container for Central Laboratory personnel use.

Data on the **SPECIMEN** case report form is entered and verified in the Data Management System by the Research Coordinator at the site around the same time as the first shipment of the specimens to the Central Laboratory.

Spec. #	Specimen Type	TRANSCOLD	TRANSDRY
1	Red top – 10 ml (<i>wrapped in aluminum foil</i>)		Stored for future testing Light sensitive 1 & 2 - Stored for future testing
2	Tiger Top – 10ml	Metabolic panel Uric acid Magnesium Phosphorus	
3	Tiger Top – 10ml		
4	Tiger Top – 10ml		
5	Blue top – 5ml		Stored for future testing?
6	Blue top – 5ml		Stored for future testing?
7	**Purple top – 5ml	HbA1C	
8	Purple top – 5ml (<i>local lab</i>)		
9	Purple top – 10ml		Homocysteine
10	Purple top – 10ml		Scantibodies
11	Purple top – 10ml	Buffy coat for DNA Lipid panel	
12	Purple top – 10ml		
13	Purple top – 10ml		
14	Purple top – 10ml		
15	Purple top – 10ml		
16	24 hr Urine		Stored for future testing
17	Nail clippings		
18	Red top		SCr – reserved for Central Laboratory

(SXLIST) - Symptoms List:

Purpose: BY completing this questionnaire the CRIC study participant records the severity of kidney disease-related problems.

Who: Participant completed, as a self-report.

When: This questionnaire is completed at:
Baseline visit (Visit 3)
12-month clinic visit (Visit 5)
24-month clinic visit (Visit 7)
36-month clinic visit (Visit 9)
48-month clinic visit (Visit 11)
60-month clinic visit (Visit 13)

Directions: **SXLIST** is a self-reported questionnaire. Instructions for completing the questionnaire must be reviewed with the participant. The participant must have experienced the symptoms in the past month (30 days).

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

Q24: Symptoms other than the ones listed from Q1 through Q23 are noted as "Other" in Q24, with a brief description.

If the questionnaire is completed with significant assistance from the interviewer, the Research Coordinator should check the appropriate box at the end of the questionnaire.

If the interviewer administers this questionnaire to the participant at baseline visit (Visit 3) because of reading or comprehension issues, the interviewer must administer the interview to the participant at all subsequent visits to maintain consistency in administration.

The Research Coordinator should check responses for completion and legibility.

SXLIST data is entered and verified in the Data Management System.

(TRANSCOLD) - Specimen Transfer – Cold Pack:

Purpose: This case report form records specimen status during the shipping process.

Who: Completed by the 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 of the Manual of Procedures.

Processed and stored specimens listed on this case report form should be shipped to the Central Laboratory at the University of Pennsylvania no later than 72 hours after collection.

Q1: 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 Collection (**SPECIMEN**) case report form.

Seq. #: This column is shaded, indicating its use by the SDCC for internal tracking purposes.

The Research Coordinator records the status of the shipped specimens. The Central Laboratory personnel assess the condition of the received specimens by checking the information in the appropriate columns. Specimens not shipped do not require a response from the Central Laboratory.

Spec. #7: This specimen should be collected on diabetic participants at clinic visit visits only. The Research Coordinator should check "Specimen Not Available" at shipping, for non-diabetic participants.

The Research Coordinator should complete the contact information and alert the Central Laboratory by faxing the completed case report form on the day of shipping.

When the shipment is received and the condition recorded, Central Laboratory personnel will fax the completed case report form to the Research Coordinator.

The Research Coordinator enters and verifies **TRANSCOLD** information in the Data Management System after the completed case report form is faxed from the Central Laboratory.

(TRANSDRY) - Specimen Transfer – Dry Ice:

Purpose: This case report form records specimen status during the shipping process.

Who: Completed by the Research Coordinator and Central Laboratory personnel.

When: Frozen specimens are shipped to the Central Laboratory once a month based on the site schedule established by the Central Laboratory at the University of Pennsylvania.

Directions: Refer to Laboratory Procedure Manual in Appendix B of the Manual of Procedures.

Processed and stored specimens listed on this case report form are 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.

Multiple records of the case report form can be entered at a visit but between all entries the status of the availability of each aliquot must be indicated.

Q1: The Research Coordinator records the date and time when specimens were processed and frozen.

Q2: 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 Collection (**SPECIMEN**) case report form.

Seq. #: This column is shaded, indicating its use by the SDCC for internal tracking purposes.

The Research Coordinator records the status of the shipped specimens. Central Laboratory personnel assess the condition of the received specimens by checking the information in the appropriate columns. Specimens not shipped do not require a response from the Central Laboratory.

The Research Coordinator also completes contact information on the case report form and alert the Central Laboratory by faxing the completed case report form on the day of shipping.

When the shipment is received and the condition recorded, Central Laboratory personnel will fax the completed case report form to the Research Coordinator.

The Research Coordinator enters and verifies the information on **TRANSDRY** in the Data Management System after the completed case report form is faxed from the Central Laboratory.

(WITHDR) – Withdrawal:

Purpose: This case report form documents premature termination of a participant from the CRIC study at any point after the cohort and sub-cohort assignment or at completion of 60-month clinic visit.

Who: Completed by the Research Coordinator.

When: This case report form is completed at 60-month clinic visit (Visit 13) or when the participant prematurely withdraws from CRIC study and/or sub-cohort at any point after the assignment.

Directions: If the participant completes CRIC study up to the 60-month clinic visit phase, (s)he is considered a CRIC study “completer.” If the participant withdraws at any point prior to the 60-month clinic visit (Visit 13), it is considered a premature withdrawal.

Q1a: A primary reason for withdrawal should be selected from the following categories:

- Ineligible at screening 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 clinic visit; does not respond to repeated efforts to continue with clinic visit 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 should be included

Q1b: Participants who withdraw prematurely 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 Research Coordinator to review the option with the participant. A written request is preferred for discarding stored specimens.

Q1c: This item is completed for participants who withdraw prematurely prior to their 60-month annual clinic visit.

Q2: Date recorded for all participants.

Space is provided for additional comments

WITHDR is entered and verified in the Data Management System.

5.A.7. General Instructions for Administrative Case Report Forms

Administrative case report forms 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 CRIC study folder as a reminder of forms to be completed at each visit.

5.A.8. Specific Instructions for Administrative Case Report Forms

(ACRFLIST) - Administrative Case Report Forms List:

Purpose: This case report form is a list of administrative case report forms with abbreviated names, and the current versions used in the study.

Who: Developed as reference for the Research Coordinator.

When: This case report form is used as a reference tool in the CRIC study to maintain current versions of the administrative case report forms in the CRIC study.

Directions: **ACRFLIST** is updated each time a case report form on the list is updated and the Research Coordinators alerted to the update.

(BDICOMM) - Beck Depression Inventory – Comment Sheet:

Purpose: This administrative form is completed for each participant who completes the Beck Depression Inventory where Q9 is coded as "2 - I would like to kill myself" or "3 - I would kill myself if I had the chance".

Who: Completed by the Research Coordinator.

When: This case report form is used on an "as needed" basis at:
Baseline visit (Visit 3)
24-month clinic visit (Visit 7)
48-month clinic visit (Visit 11)

Directions: A participant who indicates by his/her response of having thoughts of injuring himself/herself needs to be seen by Principal Investigator or a Principal Investigator designee, a Psychologist or Psychiatrist.

BDICOMM is provided to record the steps taken by the Research Coordinator to appropriately evaluate the participant prior to ending the visit and maintained in the source documentation folder.

Information recorded in **BDICOMM** is not entered or verified in the Data Management System

(CHART 1) - Recruitment Chart:

- Purpose:** This administrative form is developed as a visit schedule and provides information on processes and case report forms administered at prescreening contact (Visit 1), screening visit (Visit 2) and baseline visit (Visit 3).
- Who:** Developed as a reference tool for the Research Coordinator.
- When:** This form provides at-a-glance information on processes administered in the CRIC study at the prescreening contact (Visit 1), screening visit (Visit 2) and baseline visit (Visits 3).
- Directions:** This case report form is a visual aid for the Research Coordinator when a potential participant agrees to the CRIC study.
- This chart may be used as a checklist to ascertain that all CRIC 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 can be maintained in the participant's CRIC study binder.

(CHART2) - Clinic visit Chart:

- Purpose:** This is an administrative form that provides information on processes and case report forms administered during follow-up phone contacts and clinic visits.
- Who:** A reference tool developed for the Research Coordinator.
- When:** This form provides information on study processes at each phone contact or clinic visit.
- Directions:** This chart is a visual aid for the Research Coordinator when a CRIC study participant is scheduled for a follow-up phone contact or clinic visit procedures for the CRIC study.
- This chart may be used as a checklist to ascertain that all CRIC study processes have been completed for a follow-up contact or a visit for the CRIC study participant.
- Header information is provided to individualize the chart for each participant and can be maintained in the CRIC study binder.

(COMM) - Comments Sheet:

- Purpose:** This form is provided to record any relevant information at a visit or a contact or information related to a case report form. It can be attached to the case report form to note additional information or used to record visit-specific information.
- Who:** Used by the Research Coordinator and/or the Principal Investigator.
- When:** This form is used on an "as-needed" basis.

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

(CTQA) - Computed Tomography – QA Sheet:

Purpose: This is an administrative case report form developed to maintain an on-going Quality Assurance log of the equipment used at the sites for Computed Tomography/Electron Beam Tomography scans in the CRIC study.

This QA sheet is developed for sites that may not have an institution-based QA log. If a QA log exists at the site, the Computed Tomography/Electron Beam Tomography technologist can substitute the institution-specific log without transferring information to the CRIC study **CTQA** case report form.

Who: Completed by the site Computed Tomography/Electron Beam Tomography technologist and a copy maintained with the site Research Coordinator and the Computed Tomography Reading Center.

When: Used when torso phantom scans are conducted every 2 weeks at a minimum; Completed case report form is sent to the to the Computed Tomography Reading Center quarterly.

Directions: **CTQA** is a Quality Assurance log that is the responsibility of the site Computed Tomography/Electron Beam Tomography technologist, to maintain the integrity of the equipment used for conducting Computed Tomography tests on CRIC study participants who are assigned to Computed Tomography/Electron Beam Tomography testing.

Site Research Coordinator is jointly responsible for the log in assuring that the site Computed Tomography/Electron Beam Tomography technologist conducts Quality Assurance activity as outlined in the Computed Tomography/Electron Beam Tomography manual. An updated copy must be available with other Quality Control documents maintained at the site.

Computed Tomography Reading Center contact information is available on the case report form if the site technologist needs assistance.

CTQA is *not* entered and verified in the Data Management System.

(DCRFLIST) - Data Case Report Forms List:

Purpose: This is a list of data case report forms with abbreviated names, and the current version numbers.

Who: Developed as a reference tool for the Research Coordinator.

When: This list is a reference tool available to the CRIC study Research Coordinators at all times during the course of the CRIC study.

Directions: This case report form is a reference tool for the Research Coordinator to maintain the current version of the case report forms to be used for the CRIC study.

DCRFLIST is updated each time a case report form on the list is updated and the Research Coordinators is alerted to the update.

(DPCS) - Data Processing Cover Sheet:

- Purpose:** This administrative form helps maintain a record of data review and entry/verification at each contact or visit.
- Who:** Completed by the Research Coordinator and/or the Data entry personnel.
- When:** Completed at each clinic visit and telephone contact involving data collection and data entry.
- Directions:** The Research Coordinator checks the box for the contact or visit for which the **DPCS** is completed. Research Coordinator and/or data entry personnel initial and date when review and entry functions are completed.

(ECGCCR) - ECG Participant ID Change Request:

- Purpose:** This is an administrative case report form to request SDCC for Participant ID (PID) change after the data is electronically transmitted to the Central ECG Reading Center.
- Who:** Completed by the Research Coordinator (or designee) or the ECG technician.
- When:** This case report form is completed on an "as needed" basis when an electronic transmission of the electrocardiogram is sent to the Central ECG Reading Center with an incorrect PID.
- Directions:** The site Research Coordinator or the ECG technician must complete the requested information on the case report form and fax it to the SDCC at (215) 573-4790. CDM staff at the SDCC will arrange for the changes to be made to the database.

Requestor's name: This item identifies the site personnel requesting the data change.

Date of change request: Record the date when the site personnel requests data change

Participant Initials: 3-character identifier as entered in the **ECGTRANS** header information.

Clinical Center: This item is a 2-digit clinical center ID, ranging from 01-07, as entered in the **ECGTRANS** header information.

Site: Site ID is a 2-digit number appended to the clinical center ID, as entered in the **ECGTRANS** header information.

Visit number: Visit number is a 2-digit number, ranging from 03-13, as entered in the **ECGTRANS** header information.

Visit Date: This is the date when the case report form was completed, as entered in the **ECGTRANS** header information.

RC ID: A 4-digit RC ID, as entered in the **ECGTRANS** header information is noted in this space.

Date test performed: Information in Q2 as recorded on **ECGTRANS** is noted in this item.

ECG Tech ID: Information in Q4 as recorded on **ECGTRANS** is noted in this item.

Incorrect Participant ID: This is the Participant ID that was registered on the electrocardiogram machine and/or **ECGTRANS** and transmitted in error to the Central ECG Reading Center.

Correct Participant ID: This item is the correction needed in the database, based on the Participant ID registered in the Data Management System at the prescreening contact (Visit 1).

ECGCCR is an administrative case report form and does not get entered in the Data Management System.

(ECGQA) – ECG Quality Review Checklist:

Purpose: This is a checklist to review quality check items on an electrocardiogram prior to transmission to the Central ECG Reading Center.

Who: Developed as a reference tool for the ECG technologist.

When: This case report form is completed at:
Baseline visit (Visit 3)
12-month clinic visit (Visit 5)
24-month clinic visit (Visit 7)
36-month clinic visit (Visit 9)
48-month clinic visit (Visit 11)
60-month clinic visit (Visit 13)

Directions: This case report form is in the form of a checklist for the ECG technician to review for quality checks. If problems are identified, the electrocardiogram is repeated and re-evaluated prior to transmission to the Central ECG Reading Center

(ECGQCCHART) – ECG Quality Control Chart:

Purpose: This case report form provides examples of readings that represent poor quality ECGs transmitted to the Central ECG Reading Center.

Who: For the ECG technologist, as a reference.

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

Directions: This case report form is a miniature reference guide on what constitutes a poor quality image for the Central ECG Reading Center. Poor quality ECGs must be repeated and re-evaluated for quality prior to transmitting to the Central ECG Reading Center.

(ECHOCL) - Echocardiography Checklist:

Purpose: This is a checklist to track views for Quality Assurance purposes, when administering echocardiogram.

- Who:** To be used by the echocardiogram technologist.
- When:** Made available when echocardiograms are administered at:
12-month clinic visit (Visit 5)
48-month clinic visit (Visit 11)
- Echocardiograms are performed on participants when identified for participation in the CRIC Plus study and this administrative form is used at the time for quality checks.
- Directions:** This case report form is in the form of a checklist for the echocardiogram technologist to adhere to the echocardiogram process and the expectation that the echocardiogram was completed as described in the protocol for Quality Assurance purposes.
- Contact Information at the ECHO Reading Center is included at the end of the checklist.
- This is an administrative case report form and not entered in the Data Management System.

(HDREV) - Health Data Review Form:

- Purpose:** This administrative form is used for initial review of a potential participant's data available through the site or Primary healthcare provider's medical records to determine general CRIC study eligibility, based on broad inclusion/exclusion CRIC study criteria.
- Who:** Completed by the Research Coordinator and/or chart reviewer at the site.
- When:** This form is completed prior to the prescreening contact (Visit 1) and may not involve direct contact with the participant.
- Directions:** Items for which information is not available in the medical record at the time of review may be left unanswered.
- Source Information: Record the source from where the information was recorded on this case report form. Multiple sources can be used for data review.
- Q4: Multiple responses can be checked to determine participant's racial background.
- Q5: Serum creatinine value may be available in the participant's medical chart.
- Q5b: The eGFR calculator is available on the CRIC study website and in the Data Management System. eGFR is determined by using the serum creatinine value without applying the correction factor.
- Q6: Diagnosis of diabetes mellitus should be given by a healthcare provider.
- Q7-20: "Not apparent" response is checked if the medical chart does not contain the information sought. Screening information that becomes subsequently available allows the Research Coordinator 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 Research Coordinator can arrange for the participant to be contacted for prescreening (Visit 1).

This case report form contains confidential participant information and must not be shared with the SDCC. It should be maintained and filed in a confidential folder and stored in a locked cabinet.

HDREV data is not entered in the Data Management System.

(HPCONT) - Healthcare Provider Contact information:

- Purpose:** This administrative form maintains contact information on participant's healthcare provider(s). This information is used to share clinical observations and test results with the participant's healthcare provider if (s)he consents at the start of the study.
- Who:** Completed by the Research Coordinator or designee.
- 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 should 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 case report form.

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

This case report form contains confidential participant information and must not be shared with the SDCC. It should be maintained and filed in a confidential folder.

(PTCONT) - Participant Contact Information:

- Purpose:** This form helps maintain participant's contact information to facilitate periodic visits or contacts.
- Who:** Completed by the Research Coordinator or designee.
- When:** This form is completed at screening visit (Visit 2) and updated at each telephone contact and clinic visit thereafter.
- Directions:** Attempt must 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, a new case report form is completed.

This case report form contains confidential participant information and must not be shared with the SDCC. It should be maintained and filed in a confidential folder at the site.

(OFFSTQA) – CRIC Accuracy Check for Portable Scale:

- Purpose:** This case report form is developed as a log for the Research Coordinator to track the portable scale for quality assurance prior to conducting the off-site visit.

- Who:** Research Coordinator.
- When:** Each time a portable scale is used for measuring weight at an off-site visit.
- Directions:** Instructions for the use of the portable scale are available in the off-site visit manual in Appendix H. A log of the quality assurance check will be maintained at the site.

(PTIDLOG) - Participant ID Log:

- Purpose:** This is a list maintained at the CRIC site to assign participant ID numbers to participants who are contacted for the purpose of completing the Prescreening Information (**PRESCR**) case report form, regardless of whether they qualify for the cohort.
- Who:** Research Coordinator.
- When:** Participant ID is recorded in the **PTIDLOG** prior to the prescreening contact (Visit 1).
- Directions:** Every participant who is contacted to complete the Prescreening Information (**PRESCR**) is listed on the **PTIDLOG** and given a Participant ID number (PID) which is subsequently used for identifying the participant for the remainder of his/her contact with the CRIC study.
- Participant ID once assigned cannot be deleted or re-used for another participant.

(SCRIPT1) - Prescreening Script:

- Purpose:** This script disseminates information about the CRIC study to the participant at the prescreening contact (Visit 1) in a consistent manner. It is also used to obtain verbal consent from the participant when collecting prescreening information to determine eligibility.
- Who:** Used by the Research Coordinator or the CRIC study recruiting staff at the site.
- When:** Used at prescreening contact (Visit 1) only.
- Directions:** This site-specific script is 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**) case report form.
- This script contains confidential participant information and must not be shared with the SDCC. It should be maintained and filed in a folder along with the signed Informed Consent for enrolled participants, separate from the participant's research data.

(SCRIPT2) - Prescreening-Exclusion Script:

- Purpose:** This script is a tool developed for the Research Coordinator and is used when excluding a potential participant at the prescreening contact by answering their questions with sensitivity and consideration.
- Who:** Used by the Research Coordinator or the CRIC study recruiting staff at the site.
- When:** Used at prescreening contact (Visit 1) only.

Directions: When the participant is not considered qualified for participation, (s)he may have questions about why (s)he can't participate. The research coordinator must use tact and sensitivity in declining the participant without revealing the specifics of the CRIC 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**) case report form.

(TRANS) - Participant Transfer:

Purpose: The SDCC and the Receiving site are formally notified by completing this case report form when a participant transfers from one CRIC site to another during the follow-up phase in the CRIC study.

Who: Completed by the Research Coordinator or designee.

When: When a participant transfers to a CRIC site within the network.

Directions: The Originating site completes page 1 of this case report form and includes a copy of **TRANS** with the participant's CRIC 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 case report form 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 transfer to another site during the recruitment/enrollment phase of the CRIC study.

5.A.9. Visit-specific Administrative Case Report Forms

Purpose: These case report forms provide a list of processes and corresponding case report forms and supplies needed for screening, baseline and all follow-up visits. These case report forms can be considered as source documentation for the visit.

Who: Completed by the Research Coordinator or designee.

When: These administrative forms are developed as reference tools or source documentation, to be used at baseline and follow-up visits.

Directions: These case report forms are reference tools for the Research Coordinator to complete CRIC study procedures at each contact or visit. 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 Research Coordinators.

These case report forms are updated each time an amendment is made for the contact or visit.

These case report forms are not entered in the Data Management System.

(BASECL) - Baseline Visit Checklist/Progress Notes

(PRESCRCL) - Prescreening Visit Checklist/Progress Notes

(SCRCL) - Screening Visit Checklist/Progress Notes

(V4CL) - Six Month Clinic visit / Visit #4 Checklist / Progress Notes

(V5CL) - Twelve Month Clinic visit / Visit #5 Checklist / Progress Notes

(V6CL) - Eighteen Month Clinic visit / Visit #6 Checklist / Progress Notes

(V7CL) - Twenty-four Month Clinic visit / Visit #7 Checklist / Progress Notes

(V8CL) Thirty Month Clinic visit / Visit #8 Checklist / Progress Notes

(V9CL) - Thirty-six Month Clinic visit / Visit #9 Checklist / Progress Notes

(V10CL) Forty-two Month Clinic visit / Visit #10 Checklist / Progress Notes

(V11CL) – Forty-eight Month Clinic visit / Visit #11 Checklist / Progress Notes

(V12CL) Fifty-four Month Clinic visit / Visit #12 Checklist / Progress Notes

(V13CL) – Sixty Month Clinic visit / Visit #13 Checklist / Progress Notes

5.A.10. Submission of Case Report Forms 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 case report form or visit packets for any CRIC study participants at any time during the course of the study. Copies of case report forms could be requested for several reasons, including data auditing and case report form completion review.

If a request is made:

- The site is responsible for making photocopies of all requested case report forms.
- The original case report forms should remain in the participant's CRIC 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 case report forms should be stapled and the visit packet should be paper-clipped together.
- 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 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 and the study biostatisticians 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 Data Management System.

5.B.1.b) Missing Fields

Collected data should be reviewed for completeness at the sites prior to entry and verification. A data field on a case report form that is left blank in the application is logged as an error by the Data Management System and will be queried; e.g., if a medical history question was left blank, the Research Coordinator can inform the SDCC (in the same format as the query is 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 Research Coordinator must 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, the laboratory test order may indicate CBC but not differential. Therefore, when completing the **LABCBC** case report form, the data fields for Eosinophils, Basophils, Neutrophils, Monocytes and Lymphocytes are left blank. When this missing information 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 Q1a on **MEDHX** case report form should only be answered if participant was diagnosed in the past with cancer. If “types of cancer” is coded and the participant has not been diagnosed with cancer, a query is 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 is generated because the field should **not** be blank.

If a skip pattern query is sent to the Research Coordinator, and a change is warranted, the case report form 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 Research Coordinator should confirm data that is queried in his/her response to the SDCC. A copy of the case report form 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 “N/A” to female-oriented questions, and women should respond “N/A” 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. Biostatisticians and Data Management staff at the SDCC manually view the data and queries are sent for data that look incomplete or appear to conflict with the design of the CRIC study. The Research Coordinators should manage these queries in a similar manner as outlined above for the database-generated queries. If changes are necessary, a faxed or e-mailed response with the corrected case report form is 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.
- **CRIC Study Procedures** – Withdrawal, Data Entry and Verification Status.

5.B.3. Managing Queries

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

Queries are sent via email, and 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 Research Coordinator should print all queries e-mailed by the SDCC. At sites with more than one Research Coordinator, the lead Research Coordinator will inform the SDCC at the start of the CRIC study how they would like to receive the queries – whether one Research Coordinator at the site receives all queries or the RC ID on the case report form determines who receives the queries.
- The Research Coordinator(s) is responsible for identifying the correction to be made or providing an explanation. SDCC Data

Management staff is available to assist the Research Coordinators 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 case report form (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 CRIC 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.

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

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**.

EVENT case report form is completed once only for each phone and clinic visit. An alert-based event can be noted on the case report form or in the source document/comments sheet and the details can be probed later with the participant at the upcoming visit.

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: <ul style="list-style-type: none"> ▪ Systolic BP > 180 ▪ Diastolic BP > 110 	Immediate* or Urgent	*As assessed by clinical evaluation at the time of the BP measurement
Acute Distress including: <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ Severe aortic stenosis ▪ Aortic dissection ▪ Vegetation ▪ Tumor ▪ Cardiac tamponade ▪ LV thrombosis 	Immediate	<ul style="list-style-type: none"> ▪ Local review by technician during procedure or within 24 hours ▪ Central reading within 8 weeks

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.

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**. **If relevant event information is received between scheduled visits, record this information in the participant record/chart and add it to the EVENT form completed during the next CRIC visit or phone contact.**

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: <ul style="list-style-type: none"> ▪ 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 mg/dL 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: <ul style="list-style-type: none"> ▪ 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 72 hours

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.A.3. E-mail Urgent Alert Notification

Based on the transfer of laboratory specimens from the clinical site to the CRIC Central Lab and into the CRIC Data Management System, an automated email message will be delivered to the group of designated personnel at each site who are responsible to monitor this information. In response to receipt of an email alert message, a member of the clinical site team should initiate contact with the participant and or their primary care physician as described in the section above. It is important to provide current information to the Central Lab and SDCC as to the study personnel who will receive email Urgent Alert notices. In the absence of alert values, an email message is automatically generated to indicate that the laboratory results have been transferred and that there are no alert values for that date.

Laboratory email alerts are based on the results of the following lab parameters in the message below:

Subject: CRIC 0402 ALERTS:040527:1
 Date: Thu, 27 May 2004 15:21:35 -0400 (EDT)
 From: Shawn Ballard <sballard@shiva.cceb.med.upenn.edu>
 To: jtopf@kidometer.com, sballard@cceb.upenn.edu, spspnhp@aol.com

```
04020079 26-MAY-2004 POTASSIUM 6.1
*****
* Alerts Defined as: *
* Potassium >= 6 mEq/L OR <= 3.0 mEq/L *
* Sodium < 125 mEq/L OR > 155 mEq/L *
* Bicarbonate < 15 mEq/L OR > 40 mEq/L *
* Calcium < 6.5 OR > 13.5 mg/dL *
* Glucose < 50 mg/dL OR > 350 mg/dL *
*****
```

6.B. Summary Reporting of CRIC Study Information

6.B.1. Reporting Study Values to Participants and Health Care Providers

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

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
 - Chemistry lab values (including metabolic panel and lipid profile)
 - CBC
 - Urinary protein total
 - Estimated GFR using the modified MDRD equation
 - ¹²⁵I-GFR (as available on subcohort participants)

Baseline Report Content:

- The primary report will be available in the Data Management System approximately eight weeks after the Baseline Visit and will include results of the screening laboratory tests, serum creatinine and glucose. It will include many of the physical measures and lab results collected during the Baseline Visit.
- A **secondary** report will be available in the Data Management System approximately five months after the Baseline Visit and tests. This report will include outstanding laboratory results.

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 CRIC Study Reports

Baseline Reports – Primary and Secondary

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.

Annual 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. 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.

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.

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.

Additional Reports

CRIC participants and their health care providers will receive a report of echocardiograms and EBT/MSCT studies performed as part of the CRIC Study standard measures.

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.B.4. Inquiries Regarding Lab Results in Participant and HCP Reports

In order to streamline the process of investigating missing lab results, the following procedure has been implemented to retrieve laboratory information efficiently. After generating a report about which there are questions regarding missing results or results that appear to be erroneous, print this report, de-identify it (if the name is on it) and fax it to the central lab with a copy to the SDCC Data Management group.

This will assist lab personnel and data managers to identify exactly what the report contains. If a report cannot be generated a different investigation will occur than if there are missing or confusing results. It will also provide the visit date and the specific values in question. The SDCC will respond as soon as possible but it may take a few days to check all of the places through which a specimen moves.

PROCEDURAL OUTLINE:

- Generate a primary, secondary or follow-up report and print it.
- Obscure the name and add the ID #.
- Circle the value(s) that are in question.
- Complete fax sheet and send to 2 fax numbers.

A few helpful reminders:

- Before sending requests for missing lab results, check that the samples for results you are expecting have been sent to the lab.
- Check the calendar to ensure that expected results are within the time frame for appearance in the data management system.
- The Year 1 report (Visit 5) and all subsequent annual reports will consist of a single report only.
- Completely obscure the name and write the ID# clearly at the top of the report.
- The appearance of 'xxx' in the Urine Protein results column means that "the amount of protein found in the urine was negligible." The 'xxx' in the results column for values other than urine protein means that "the specimen was inadequate and tests could not be run."

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 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. Establishing a CRIC DMS Account

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, contact information, 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 SDCC Project Manager will contact the user with his/her account information.

IMPORTANT NOTE: It is the responsibility of the clinical site to notify the SDCC when an employee has been terminated and should no longer have access to the CRIC Study DMS. 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.A.2. 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:
- ◆ IP Address: 128.91.204.84
- ◆ http://ssd1.cceb.med.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.3. 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:

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.

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.

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.

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.

Central Reading Transfer Entry

- ◆ Allows for entry of the CTRANS and ECHOTRANS forms.
- ◆ Requires Clinical Center number, Site number, Visit Number, and Transfer date.
- ◆ Allows browsing to confirm data entry status.
- ◆ Allows entered data to be viewed without edit.

Diet*Calc Analysis Results

- ◆ Generates a report that assesses the dietary factors associated with cardiovascular disease progression in renal insufficiency.

EBT/CT Scan Results

- ◆ Generates results from the Electron Beam Tomography (EBT)/Cardiac CT scan.
- ◆ Requires Clinical Center number, Site number, and RCID.

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).

Link to CRIC Web Site

- ◆ Provides a hyperlink directly to the CRIC web site home page.

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.

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.

View Study Alert

- ◆ Allows sites to view participants lab results from the Central Laboratory at the University of Pennsylvania.
- ◆ This module also allows the sites to view any lab results that are consider alerts based on the CRIC protocol.
- ◆ Requires Clinical Center number, Site number, and RCID.

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.

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.

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:

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.

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.

Mandatory Fields (neither field may be left blank):

- Participant ID
- Participant Initials

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.

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.

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:**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.

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).

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:**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.

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.

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.

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:

Enter Key fields:

- (header information as outlined in the previous section - Prescreening, Screening, Baseline and Follow-up CRF Entry)

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.

“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:

Enter key fields

- (header information), as outlined in Section 7D (Prescreening, Screening, Baseline and Follow-up CRF Entry.)

“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.

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.

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.

- After the last CRF has been entered and verified for the current participant, the entry process can be repeated for the next participant.
- 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.
- 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:

- The DMS provides assignment information that is recorded on the paper CRF by the user.
- 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.
- If the participant appears ineligible, a message displayed on the screen indicates reasons.

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:

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.
- 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 of 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:

Two possible ways to obtain an eGFR value:

- Entering a Participant ID that has completed screening and registration.
- Entering the Key Variables (Serum Creatinine, age, gender and race).

Entering Participant ID:

- 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.

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.

Entering the Key Variables:

- eGFR value may also be obtained by entering the key data used for the calculation.
 - ◆ 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:

- Click on the “Medication Reference Tool” button in the DMS.
- 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.
- Click on “Execute Query” and select the most representative coding for the reported medication.
- If the site personnel are unable to locate a medication, SDCC/CDM personnel may be contacted to assist with determining the numerical coding.
- Use the ‘Tab’ key to automatically insert a new row when listing medications.

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:

-

7.K.1. Healthcare Provider/Participant Baseline Report

All site personnel with data entry privileges [username and password assigned by the SDCC helpdesk] will be able to generate reports. **A valid RC ID # is required to generate a report for protection of participant information.**

This report is a compilation of data from several CRFs and electronic sources. When laboratory specimens are sent to the Central Laboratory, an appropriate amount of time should be allowed for specimen analysis and transfer of results.

- Results for the primary reports (metabolic and lipids panels) at baseline are available within 8 weeks from the time the specimens are sent to the Central Laboratory at the University of Pennsylvania.
- Results for the secondary reports at baseline (phosphorus, magnesium, homocysteine, intact parathyroid hormone - whole and intact) are available within 5 months from the time the specimens are sent to the Central Laboratory at the University of Pennsylvania.
- Results for the primary reports (metabolic and lipids panels) at annual visits are available within 8 weeks from the time the specimens are sent to the Central Laboratory at the University of Pennsylvania.

To generate primary or secondary report, the following steps should be followed:

- Log on to the Data Management System using your personal username and password provided by the SDCC.
- Click on Forms and Reports module.
- Click on the button to select Healthcare Provider or Participant Report.
- Enter the relevant participant and healthcare provider information requested on the screen.

Patient ID: CRIC Participant ID

Patient Name: First and Last Name of the participant as reported on the informed consent

Center and Site: IDs assigned to the primary clinical centers and sites as identified in the protocol

RC ID: 4-digit RC ID registered in the Data Management System

Report Date: In "mm/dd/yyyy" format.

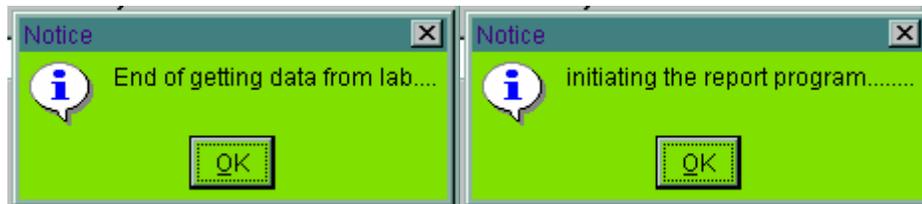
Provider: Healthcare Provider name to be used to address the HCP report.

Note: Data displayed on the screen is not saved in the database, and is used to populate relevant information for the HCP or Participant report only.

Site personnel with 4-digit registered RC IDs in the Data Management System have access privileges to generate these reports.

Click on “Generate the Report” button.

- A series of checks within the DMS will retrieve the data for the report.
- Continue to click on the “OK” buttons.
- A message box will indicate that the data has been retrieved and the report is being generated.

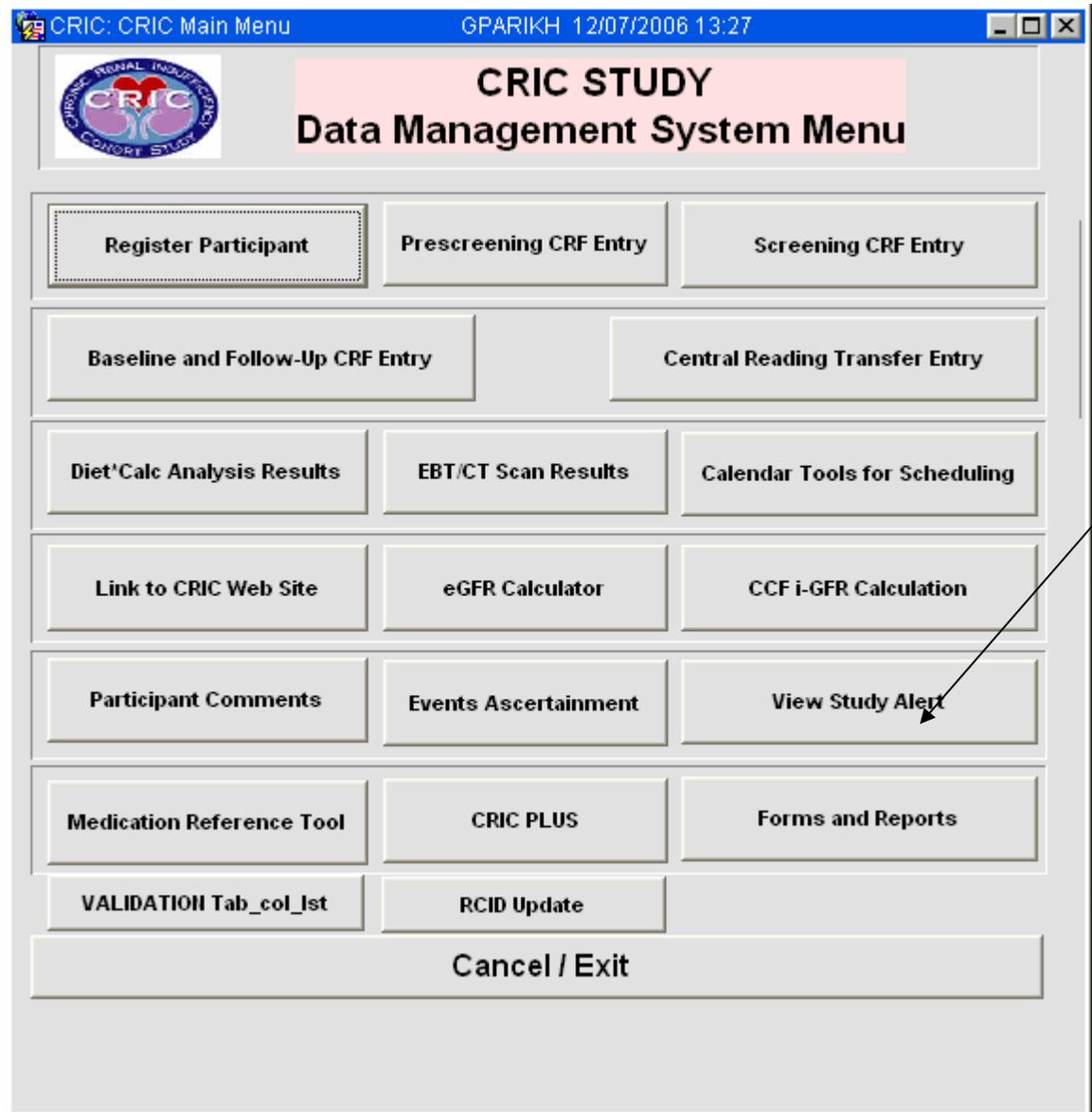


- Netscape will launch the report as a PDF file.
- Select “File” and “Print” from the menu to print the report.
- Note: Some of the results may not be available immediately.

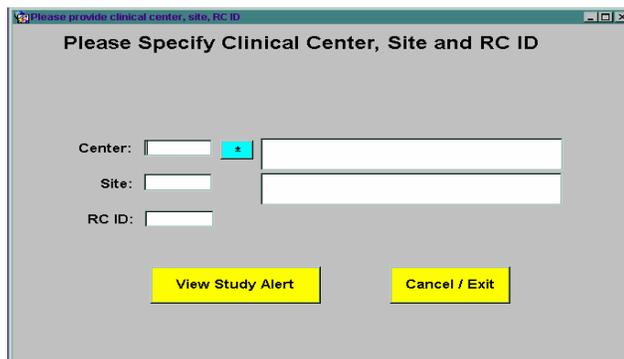
7.K.2. View Study Alert

To view study alerts:

- Log on to the Data Management System using your personal username and password provided by the SDCC.
- Click on “View Study Alerts” module.



- Enter the information requested on the screen.



- Click on "View Study Alert" button.

- A worksheet appears with a list of available physical measures and laboratory data.
- This list also indicates if laboratory data has “alert” values in the last column.

This worksheet can be printed for participant files.

Clinical Center	Site	Participant ID	Initials	Demographics	Blood Pressure	Ankle Brachial Index	Kidney Function Tests	Metabolic Panel	Lipid Tests	Complete Blood Count	ALERT
D1	01	01010001	APS	06/04/2003	06/19/2003	06/19/2003	06/19/2003	06/19/2003	06/19/2003	06/19/2003	YES
01	01	01010005	YBV	06/18/2003	06/18/2003						
01	01	01010006	JXR	06/20/2003	07/21/2003	07/21/2003		07/21/2003	07/21/2003	07/21/2003	
01	01	01010007	MHB	06/25/2003	07/31/2003	07/31/2003	07/31/2003	07/31/2003	08/01/2003	07/31/2003	
01	01	01010008	FRK	06/26/2003	07/10/2003	07/10/2003	07/28/2003	07/10/2003	07/10/2003	07/10/2003	YES
01	01	01010011	RTM	07/03/2003	08/19/2003	08/19/2003		08/19/2003	08/19/2003	08/19/2003	YES
01	01	01010012	LXM	07/22/2003	09/10/2003	09/10/2003		09/10/2003			
01	01	01010013	EJP	07/02/2003	08/14/2003	08/14/2003	09/23/2003	08/14/2003	08/14/2003	08/14/2003	YES
01	01	01010015	DRN	07/08/2003	08/05/2003	08/05/2003	08/05/2003	08/05/2003	08/05/2003	08/05/2003	
01	01	01010016	FJB	07/08/2003	09/11/2003	09/11/2003	09/11/2003	09/11/2003	09/11/2003	09/11/2003	YES
01	01	01010021	FXL	08/21/2003	10/30/2003	10/30/2003		10/30/2003		10/30/2003	
01	01	01010022	DJD	07/22/2003	09/13/2003	09/13/2003	09/13/2003	09/13/2003	09/13/2003	09/13/2003	
01	01	01010028	JOB	07/18/2003	09/08/2003	09/08/2003	10/15/2003	09/08/2003	09/08/2003	09/10/2003	
01	01	01010029	JCM	07/23/2003	08/27/2003	08/27/2003	08/27/2003	08/27/2003	08/27/2003	08/27/2003	
01	01	01010031	VHG	07/24/2003	09/18/2003	09/18/2003	09/18/2003	09/18/2003	09/18/2003	09/18/2003	YES
01	01	01010032	YDB	07/29/2003	07/29/2003						
01	01	01010033	LXT	07/30/2003	10/30/2003	10/30/2003		10/30/2003		10/30/2003	
01	01	01010034	JAR	08/01/2003	09/25/2003	09/25/2003		09/25/2003		09/25/2003	
01	01	01010035	FXG	08/13/2003	10/22/2003	10/22/2003		10/22/2003		10/22/2003	
01	01	01010037	CEB	08/08/2003	11/07/2003	11/07/2003		11/07/2003		11/07/2003	YES

- An option is presented to generate a report from this screen or view laboratory data, including “alert values.”
- Select the PID and click on “View Laboratory Data” button.
- CRIC study-related list of laboratory results from the Central Laboratory at the University of Pennsylvania appear with specimen collection date, date of measure, units of measure, reference ranges and “out-of-range” indicator, which indicates if the values were high or low compared to the reference range.

This worksheet can be printed for participant files.

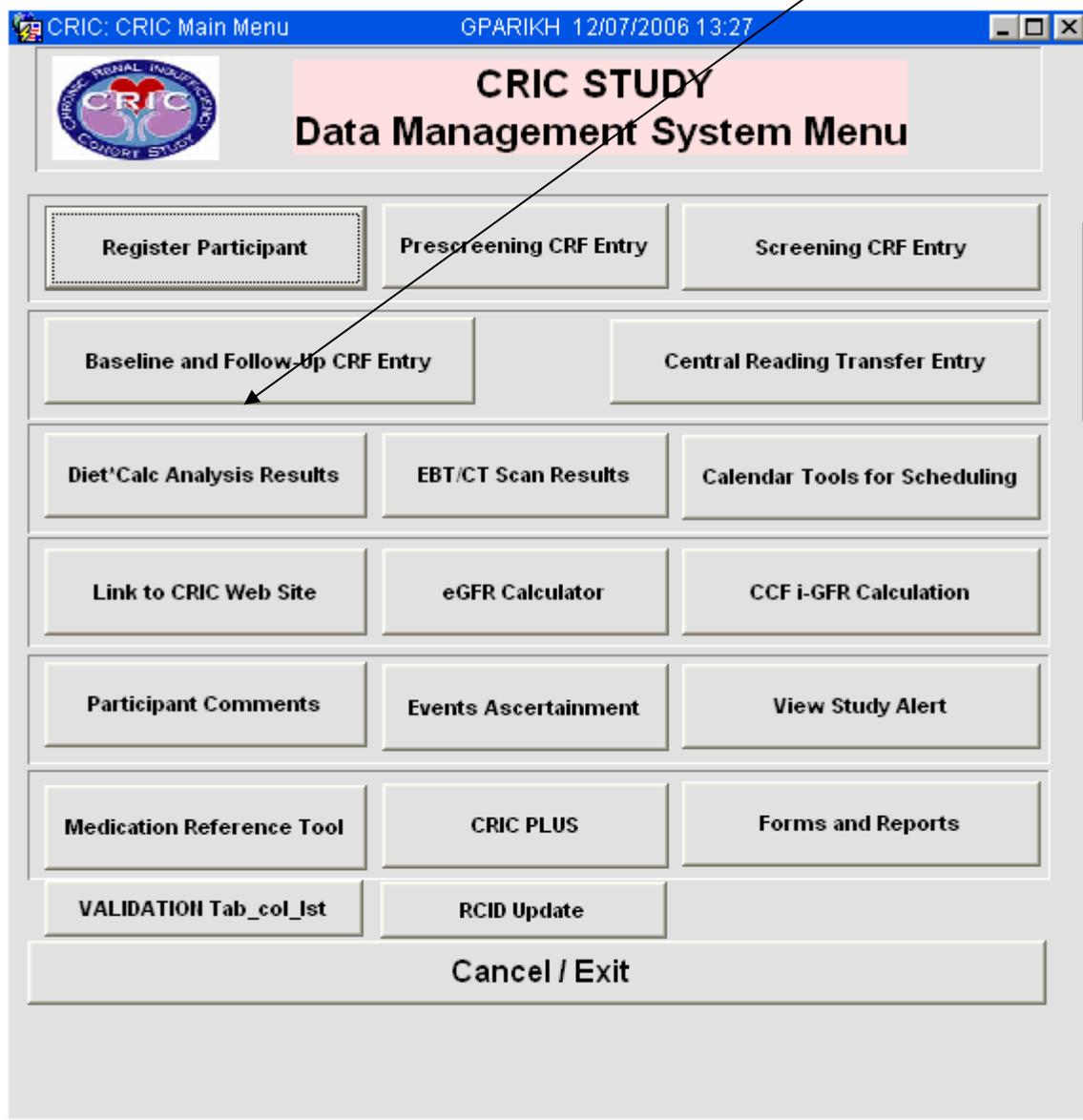
Name of Measure	Lab Test Code	Specimen Collection Date	Laboratory Result	Unit of Measure	Measure Range	Date of Measure	Out of Range Indicator
GLUCOSE	1000020	06/19/2003	130	mg/dL	70-110	06/20/2003	H
UREA NITROGEN	1000025	06/19/2003	22	mg/dL	10-20	06/20/2003	H
CREATININE, SERUM	1000030	06/19/2003	1.4	mg/dL	0.8-1.3	06/20/2003	H
SODIUM	1000035	06/19/2003	136	mmol/L	133-143	06/20/2003	
POTASSIUM	1000040	06/19/2003	4.3	mmol/L	3.5-5.3	06/20/2003	
CHLORIDE	1000045	06/19/2003	100	mmol/L	97-107	06/20/2003	
CO2 CONTENT	1000050	06/19/2003	27	mmol/L	22-30	06/20/2003	
CALCIUM	1000060	06/19/2003	8.6	mg/dL	8.5-10.5	06/20/2003	
ALBUMIN	1000085	06/19/2003	3.5	g/dL	3.5-5.8	06/20/2003	
TOTAL PROTEIN	1000095	06/19/2003	6.8	g/dL	6.1-8.5	06/20/2003	
ALKALINE PHOSPHATASE	1000105	06/19/2003	43	U/L	35-125	06/20/2003	
TOTAL BILIRUBIN	1000110	06/19/2003	0.4	mg/dL	0.0-1.2	06/20/2003	
ALANINE AMINOTRANSFERASE	1000135	06/19/2003	26	U/L	21-72	06/20/2003	
ASPARTATE AMINOTRANSFERASE	1000140	06/19/2003	39	U/L	17-59	06/20/2003	
TROPONIN-I	1000148			ng/mL	0.0-2.0		
CREATININE CLEARANCE	1000266	06/19/2003	46	mL/min	80-120	06/23/2003	L
URINE TOTAL VOLUME	1000270	06/19/2003	2800	mL	800-1800	06/23/2003	H
URINE CREATININE MG/G	1000400	06/19/2003	32.9	mg/dL		06/23/2003	R
URINE CREATININE G/T	1000405	06/19/2003	0.92	g/TV	0.80-2.80	06/23/2003	
URINE PROTEIN MG/DL	1000470			mg/dL			

Lipid Profile			
Total Cholesterol	06/19/2003	101	mg/dL
Triglycerides	06/19/2003	168	mg/dL
HDL Cholesterol	06/19/2003	65	mg/dL
LDL Cholesterol	06/19/2003	77	mg/dL

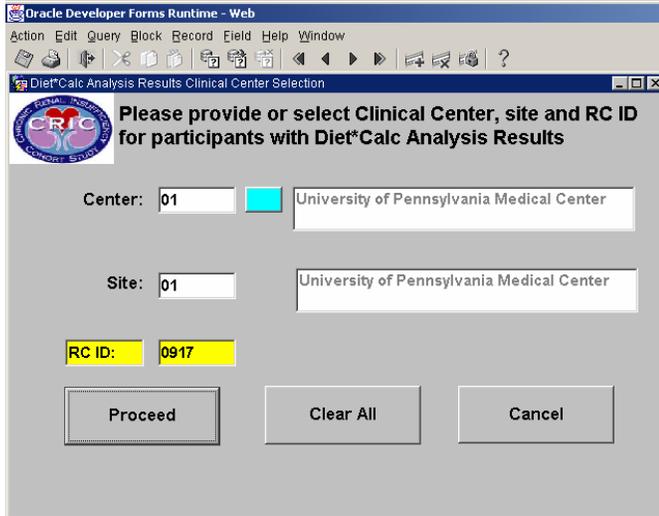
7.K.3. DHQ Reports

Questions related to the contents of the DHQ report must be directed to Dr. Anderson for clarification.

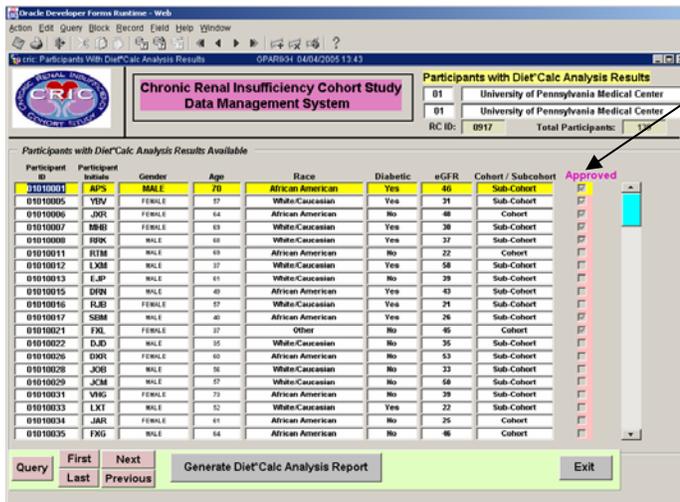
- Log on to the Data Management System using your personal username and password provided by the SDCC.
- Select and “double click” on Diet*Calc Analysis Results button from the Main Menu screen.



- Enter the requested information (CC ID, Site ID, RC ID) on the first screen that pops up and click on “Proceed”.



- A list of Participant IDs with relevant demographic characteristics will be visible on the next screen for available DHQs.
- DHQs reviewed by Dr. Anderson, with a checkmark in the “Approved” column, are available for report generation.
- Select a Participant ID with a DHQ report that is reviewed by Dr. Anderson and click on the “Generate Diet*Calc Analysis Report” button at the bottom of the screen.



- Enter “Patient Name” and “Report Date” (**date of report generation**) and click on “Generate Diet*Calc Analysis Report” button at the bottom of the screen and the system will generate the DHQ report and a letter to the participant.

Oracle Developer Forms Runtime - Web

CRIC Diet*Calc Analysis Report Request

Please Specify Patient ID, Patient Name, Report Date for Diet*Calc Analysis Report

Patient ID: 01010001

Patient Name: ABC

Center: 01 University of Pennsylvania Medical Center

Site: 01 University of Pennsylvania Medical Center

Report Date: 04/04/2005 (MM/DD/YYYY)

RC ID: 0917

Generate Diet*Calc Analysis Report Nutrient Glossary List

Clear / Reset Cancel / Exit

- System checks for the availability of the report.

Oracle Developer Forms Runtime - Web

CRIC Diet*Calc Analysis Report Request

Please Specify Patient ID, Patient Name, Report Date for Diet*Calc Analysis Report

Patient ID: 01010001

Patient Name: ABC

Center: 01 University of Pennsylvania Medical Center

Site: 01 University of Pennsylvania Medical Center

Report Date: 04/04/2005 (MM/DD/YYYY)

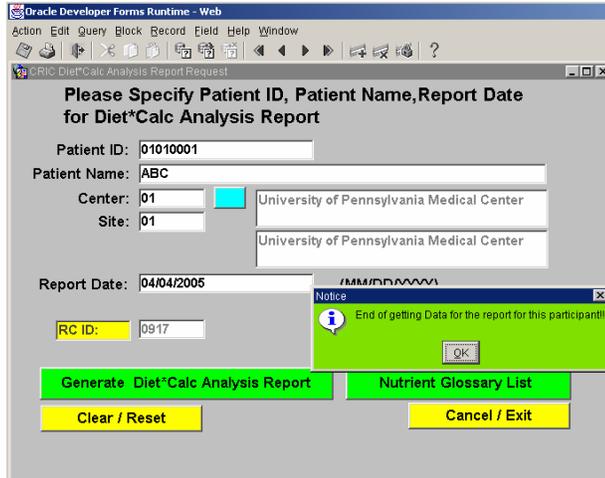
RC ID: 0917

Generate Diet*Calc Analysis Report Nutrient Glossary List

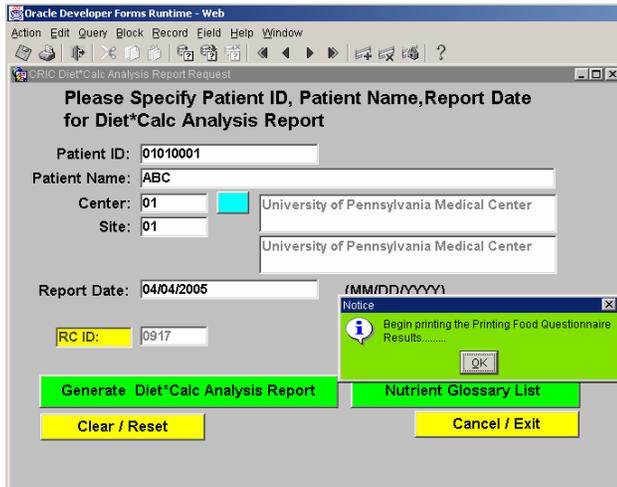
Clear / Reset Cancel / Exit

Notice
Retrieving Diet*Calc Analysis results for the participant 01010001.....
OK

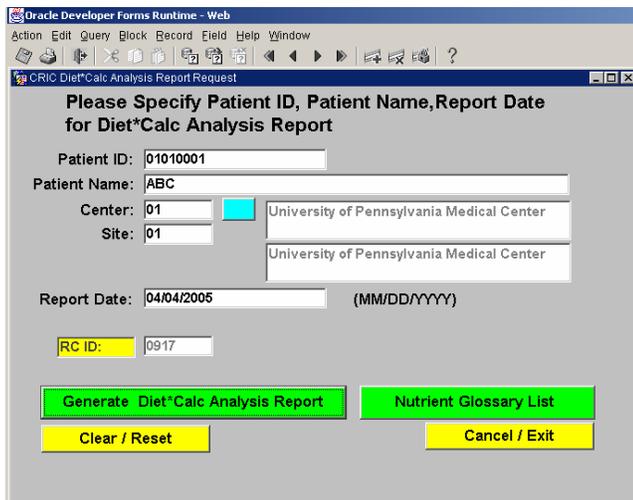
- Click "OK".
- System finds the report.



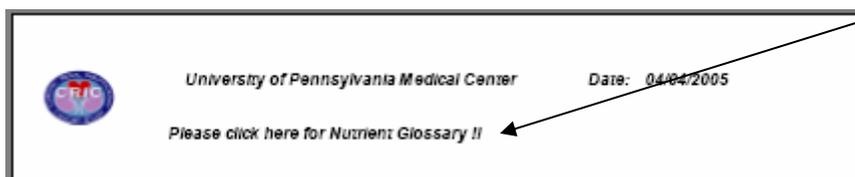
- Click “OK”.
- System gets ready to display report in PDF format.



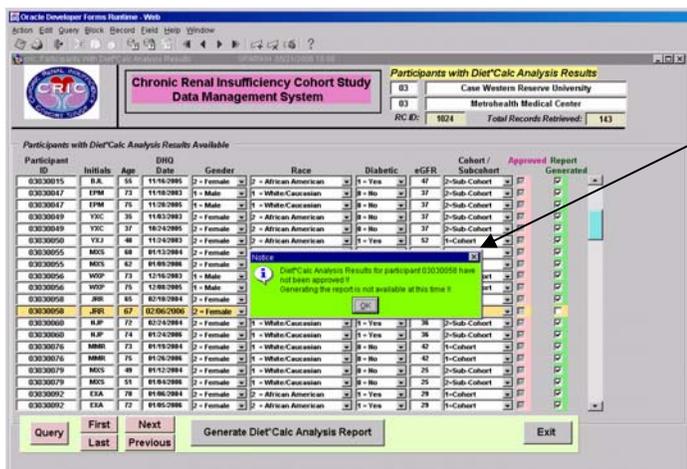
- Click “OK”.
- Print report.



- “Nutrient Glossary List” explains the functions of different nutrients in the body and can be accessed either by clicking on the button (see above) or clicking on the link on page 3 (see below).



- If an attempt is made to generate a report that has not been reviewed by Dr. Anderson, an error message will remind and prevent the user from generating the report.



Dr. Anderson’s Contact Information

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 Epidemiology, and Clinical Research
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 Fax: 410-955-0476

7.K.4. CTRANS and ECHOTRANS Data Entry

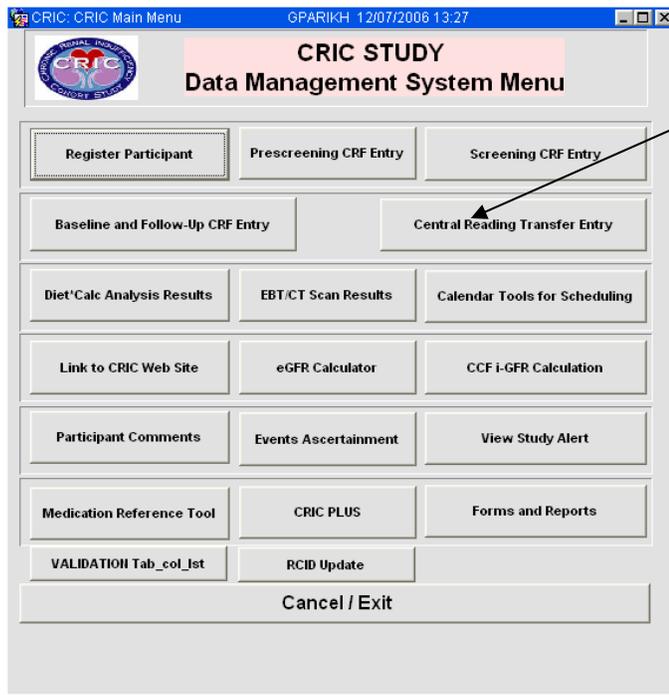
When Computer Tomography (CT) scans or Echocardiography (ECHO) readings are sent to Central Reading Center, transfer sheets (**CTTRANS** or **ECHOTRANS**) **must** be sent with the shipment.

CT Central Reading Center will fax CTRANS back to the sites as an acknowledgement that the scans are received. The site must enter the CRF data in the DMS **after** the acknowledgement is received.

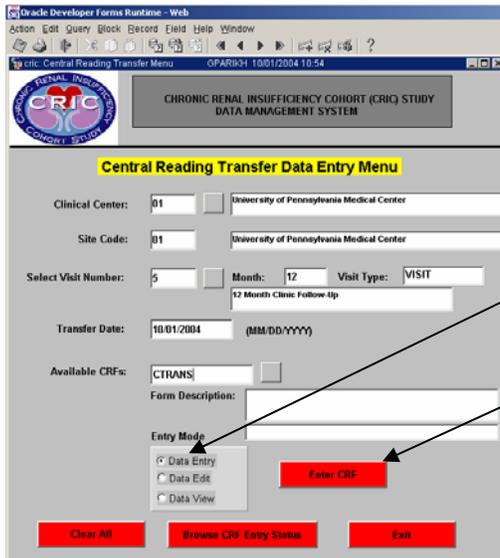
ECHO Central Reading Center must also receive the transfer CRF (**ECHOTRANS**) but will **not** receive an acknowledgement. The site must enter the transfer CRF immediately after the shipment.

Data entry procedure:

- Log on to the Data Management System.



- Click on “Central Reading Transfer Entry” module.
- Enter header information in the “Central Reading Transfer Data Entry Menu”, which included Center, Site, Visit Number and Transfer Date. In “Available CRFs” choose **CTRANS** or **ECHOTRANS**.



- Select “Data Entry” button in Entry Mode.
- Click on “Enter CRF”.

- For additional records (more than the 6 lines visible on the screen), use the “Tab” key on the keyboard after entry in the last cell (Transfer date field) of line #6 to create line #7.

7.K.5. EBT/CT Scan Report

- Log on to the Data Management System.

- Click on EBT/CT Scan Results.

Oracle Developer Forms Runtime - Web
 Action Edit Query Block Record Field Help Window

EBT / CT Scan Results Clinical Center Selection

Please provide or select Clinical Center, site and RC ID for participants with EBT / Cardiac CT Scan Results

Center:

Site:

RC ID:

Proceed Clear All Cancel

- Enter the relevant Center, Site and RCID codes on the screen and hit “proceed”.
- Select a PID and click “Generate EBT/Cardiac CT Scan Reports”.
- A “✓” in the “Report Generated” column indicates that the healthcare provider report and the participant report has already been generated by the site Research Coordinator.

CRIC - Participants With EBT/Cardiac CT Scan Results MDURBORO 05/17/2006 09:51

Chronic Renal Insufficiency Cohort Study Data Management System

Participants with EBT / Cardiac CT Scan Results Available

Participant ID	Initials	Visit Number	TEST CODE	TEST DATE	EBT SCORE	Report Generated
03030001	JOF	5	A	10/26/2004	344	<input checked="" type="checkbox"/>
03030003	HGA	5	A	10/21/2004	425	<input checked="" type="checkbox"/>
03030004	KID	5	A	10/20/2004	176	<input checked="" type="checkbox"/>
03030009	SAM	5	A	12/2/2004	595	<input checked="" type="checkbox"/>
03030011	MAL	5	A	10/18/2004	17	<input checked="" type="checkbox"/>
03030015	B.K.	5	A	11/2/2004	182	<input checked="" type="checkbox"/>
03030047	EPM	5	A	12/19/2004	661	<input checked="" type="checkbox"/>
03030049	TRC	5	A	11/15/2004	9	<input checked="" type="checkbox"/>
03030056	WOP	5	A	12/28/2004	213	<input checked="" type="checkbox"/>
03030060	RLP	5	A	1/12/2005	366	<input checked="" type="checkbox"/>
03030129	SJW	5	A	4/1/2005	8	<input checked="" type="checkbox"/>
03030132	AJS	5	A	5/2/2005	12	<input checked="" type="checkbox"/>
03030234	MOP	5	A	6/22/2005	8	<input checked="" type="checkbox"/>
03030239	SJP	5	A	6/16/2005	8	<input checked="" type="checkbox"/>
03030241	PRG	5	A	12/13/2005	8	<input checked="" type="checkbox"/>
03030246	WOM	5	A	10/11/2005	8	<input checked="" type="checkbox"/>
03030278	COR	5	A	1/6/2006	8	<input checked="" type="checkbox"/>
03030279	JMB	5	A	1/24/2006	8	<input checked="" type="checkbox"/>
03030306	BEL	5	A	2/15/2006	865	<input checked="" type="checkbox"/>

Participants with EBT / Cardiac CT Scan Results

03 Case Western Reserve University
 03 Metrohealth Medical Center
 RC ID: 1024 Total Records Retrieved: 19

Query First Next Last Previous Generate EBT/Cardiac CT Scan Reports Print Blank EBT Reports Exit

- To generate the EBT/Cardiac CT Scan Reports, type in the Patient’s name, Report Date in the MM/DD/YYYY format, and HCP Name.
- Hit the “Generate EBT/Cardiac CT Scan Reports” button.

- Click “OK”.
- Print report.

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

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

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).

DMS 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).

7.M.2. CRIC Study Website

The CRIC website contains the protocol, amendments, manuals, documents and reports that are not available in the DMS. Before a Steering Committee meeting the quarterly reports that will be reviewed during the meeting will be posted here. The website also contains the study CRFs.

Access to the CRIC Study website requires a different username and password than the DMS. To request an account on the website, contact the SDCC project manager. You will be notified when your account has been established. It is the responsibility of the clinical site to notify the SDCC when an employee has been terminated and should no longer have access to the CRIC Study website.

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:

- Signed/dated notation of when informed consent and HIPAA authorization were obtained (and if any questions were addressed)
- 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."
- 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."
- 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.
- Training of 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.

Quality Control Manual of Procedures and Certification

The SDCC will develop a comprehensive Quality Control Manual of Procedures that will describe the QC activities associated with the study procedures. Study personnel are expected to participate in these activities as described in the manual to indicate training and certification of study members and equipment maintenance. Clinical sites should maintain the appropriate documentation in a QC and Training file, and track this process for existing and newly hired staff.

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 Scientific Advisory Committee.

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.

9.A.2. Supplies

The nail clipper used to collect these specimens should be made of 100% stainless steel not contain any trace metals. The following products are recommend for collecting nail specimens:

- Brookstone Clip & Catch Nail Clipper
- Seki Nail clipper with Grip Handle
- Mehaz Professional Nail Clipper
- Specimen storage container for the nail clippings:
 - Same as the cryogenic vials utilized for blood collection/specimen
 - 2ml cryogenic vials – MFr# 5000-1020
 - Fisher Catalogue # 03-337-74

9.A.3. 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 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.
- When possible, it is recommended that clinical sites store these supplies for participants (in a labeled box with ID#) on site to prevent loss and control contamination.

9.A.4. 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 a 2ml specimen storage cryovial
- 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.5. 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.6. 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.
- Nail specimens may be shipped to the Central Lab with refrigerated blood and urine samples.

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]

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.
- Repeat measurement. The 2nd measurement should be within 0.5 cm of the first. Record the first of the 2 measurements. If the 2nd measurement is not within 0.5 cm of the first measurement, repeat measurement until you obtain two that are within 0.5 cm of each other. Record the first of these 2 measurements.

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. The second measurement should be within 0.1 kg of the first measurement. Record the first measurement on the CRF.
- If the difference between the 2 measurements is greater than 0.1 kg, repeat the measurement until 2 results are within 0.1 kg and record the first of the 2 measurements on the CRF.

- 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.

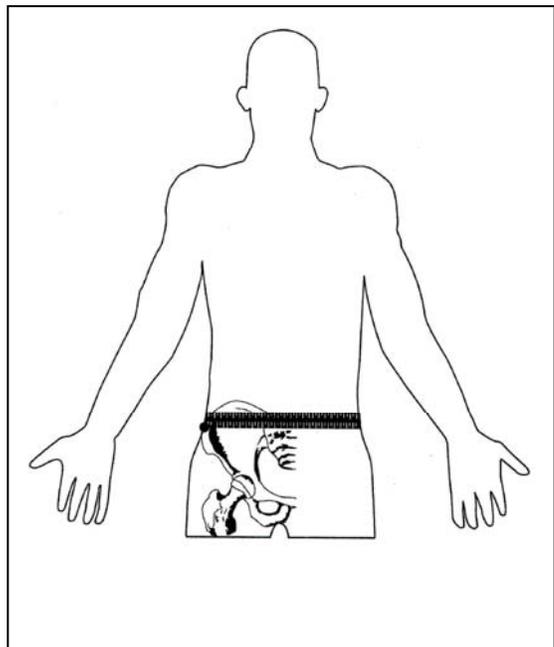
Waist Circumference

- 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.
- Repeat waist measurement. The second measurement should be within 1 cm of the first. Record the first of the 2 measurements. If the second measurement is not within 1 cm, repeat measurement until 2 results are within 1 cm. Record the first of the 2 measurements.

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

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.

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 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.

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 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.
- The Data Management System will perform the ABI calculation based on the measured values.
- Example: Calculate the ABI by dividing the higher of the 2 ankle pressures in that leg by the HIGHER (right or left) brachial systolic pressure:

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

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

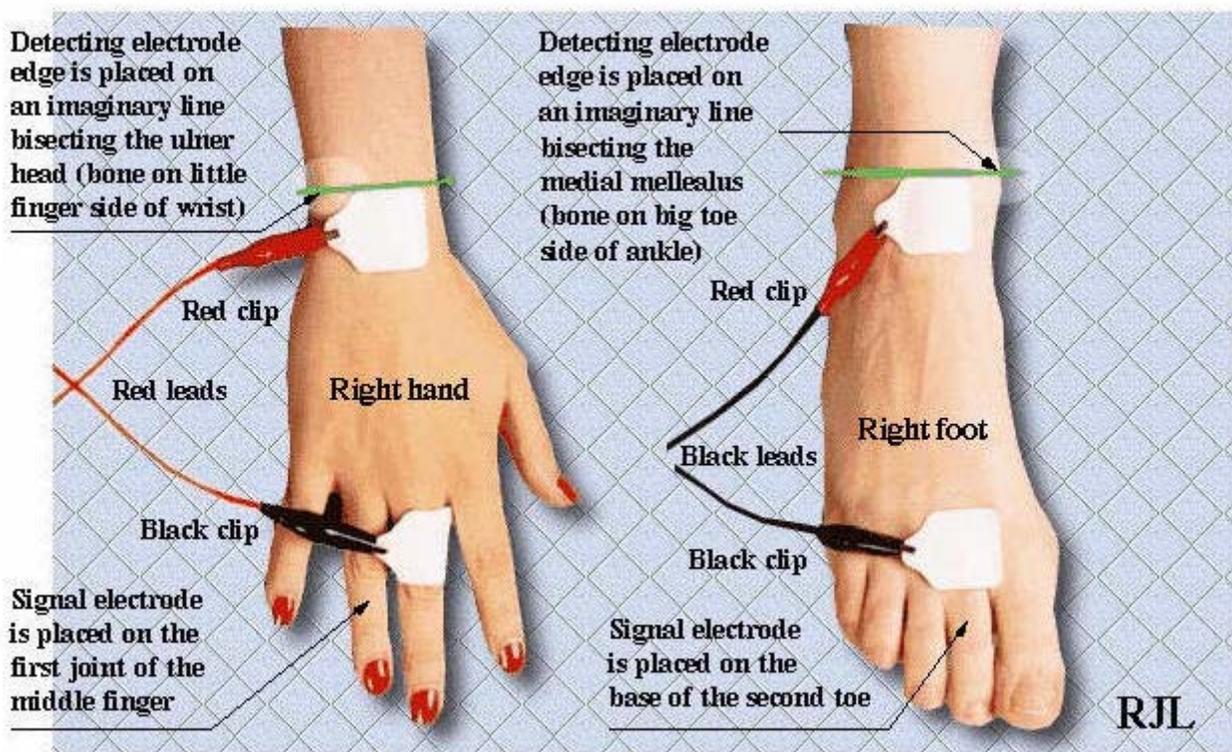
BIA is conducted at each annual visit.

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].
- **IMPORTANT NOTE:** Participants with an implanted defibrillator should NOT have this test performed. This should be indicated on the Case Report Form.

How Electrodes are Placed on the Hand and Foot BIA TESTING PROCEDURE



9.D.2. Testing Procedure

- BIA is conducted at each annual visit.

- 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.
- If jewelry can not be removed on the right side, the test should be performed on the left side. A note to this effect should be made in the Comments section of the participant chart. Repeat tests should be performed consistently on the same side.
- 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.
- NOTE: The resistance value does not lock onto a number because of muscle contractions in the heart. The reading should be the most representative number. Press the 'Reactance' button when you are ready to record this value.
- 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.

Special Considerations

- If a participant has an implanted defibrillator this test should not be performed.
- If a participant is missing limbs on both sides (i.e., the R and L legs), this test should not be performed.
- If a participant is missing a limb on the right side, perform the test on the left side and note the exception.
- If a participant is missing the designated digit (middle finger), the next finger should be used.

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 Trainers at 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.

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.

Arm measurement, cuff selection and placement should be completed prior to a five minute rest period in this quiet room. Calculation of the corrected peak inflation level and pulse is measured before taking the first 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.

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 (90 degree angle), the arm length is measured from the acromion (or boney extremity of the shoulder girdle) to the olecranon (or tip of the elbow) with a plastic coated metric tape. The midpoint is marked on the dorsal surface of the skin.
- The participant should then relax the arm straight down along the side of the body. The arm circumference is measured by drawing the tape snugly around the arm at the level of the midpoint 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.

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

Application of the Blood Pressure Cuff

- The participant should be seated with the elbow and forearm resting comfortably on a table with the palm of the hand turned upward. The area to which the cuff is to be applied must be bare.
- Fold the cuff bladder in half mating each corner of the bladder to find and mark the midpoint on the cuff cover. Do not use the permanent marking on the bladder because it may become dislocated and off center.
- The brachial artery is located by palpation and marked. 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.

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

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 mmHg. 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.

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.

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.

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.

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.

1. Wait at least 30 seconds after complete deflation of the cuff following any preceding inflation.
2. Connect the cuff to the Tycos Classic Hand Aneroid device.
3. Place the ear pieces of the stethoscope into the ears, with the tips turned forward.
4. Apply the bell of the stethoscope over the 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.
5. Using the previously determined peak inflation level, rapidly inflate to this level. The eyes of the observer should be focused on the dial of the aneroid sphygmomanometer. The observer should rapidly inflate the cuff.
6. By slightly adjusting the valve, deflate and maintain a constant rate of deflation at approximately 2 mm Hg per second. Allow the cuff to deflate, listening throughout the entire range of deflation, from the maximum pressure past the systolic reading (the pressure where the **first of two consecutive beats** is heard), until 10 mm Hg below the level of the diastolic reading (that is, 10 mm Hg below the level where the last of two consecutive beats is heard).
7. Open the valve to deflate fully and disconnect the tubing. Remove the stethoscope earpieces from the ears.
8. Record the systolic and diastolic reading.
9. Repeat steps 1 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.
10. Raise the participants arm overhead for 15 seconds without the participant's assistance. (The arm should be fully supported at the elbow and wrist by the observer.) The participant should not help to support the raised arm.

Standing Pulse and Blood Pressure Measurement

After completing 3 seated blood pressure readings, raise the bedside table at the participant's immediate right so that unnecessary movement or walking will not occur when the participant is asked to stand. The participant is then asked to stand quietly with their arms relaxed at their sides for 2 minutes.

- After 2 minutes, the blood pressure observer should raise the participants arm (fully supported overhead) for 15 seconds.
- The arm is then placed on the bedside table with the palm of the hand turned upward. The bedside table needs to be elevated so the arm can rest at heart level for the standing pulse and blood pressure. If the table can not be elevated to that height, pillows can be added to the table top to bring the arm to heart level.
- Immediately, the pulse is palpated and counted for thirty seconds and multiplied by 2 to give the full number of beats per minute and recorded on the BP case report form.
- Take one standing blood pressure measurement as described above and record the values 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.E.5. **Equipment Calibration**

Blood pressure kits may be calibrated every 6 month by the manufacturer, Welch Allyn. They will replace parts that are worn free of charge provided the equipment has a Lifetime Warranty indicated on it.

Contact the Welch Allyn service department at 1-800-535-6663. Provide the serial number (located on the dial); they will give you a repair number. Write a brief memo to include with the equipment shipment and also include these numbers in the body of the letter. Write the repair number on the FedEx form under "name". The equipment is being sent to a different location than the telephone service center.

The address is: Arden Technical Services
16 Old Charlotte Highway
Asheville, NC 28803

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**

Collect urine before venipuncture. Collect Urine from all participants whenever possible. 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

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 -20°C or -80°C.
- 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.

10.C.3. 24 Hour Urine Collection Instructions

- 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.
- During the collection process, it is recommended that the 24 hour urine sample container be stored in the refrigerator. In order to accommodate a participant's need for mobility, a portable urine collection container may be used to collect samples continuously. If it must be at room temperature for any reason, the Central Lab recommends that this time does not exceed **2 hours, at the maximum.**

Inadequate Collection

- Specimens that are less than 500 mls or collected for less than 22 hours or more than 26 hours are considered inadequate collections. If a participant returns such a sample, a second attempt should be made at this collection. The original specimen should be stored at the site in 3 frozen aliquots, in the event that a second collection attempt is not successful. If after a reasonable amount of time and urging, it seems unlikely that a second 24 hour collection will be returned to the clinical site, the original sample should be processed as follows:
 - Remove 1 aliquot from the freezer.
 - Complete a TRANSCOLD form for the urine specimen.
 - Send to the Central lab. The specimen will thaw in transit.

- Send the remaining 2 frozen aliquots with the TRANSDRY shipment.

10.C.4. “Clean-Catch” Urine Proteomics Sample Collection

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. This sample is being collected for future studies and will be processed for storage shortly after collection. The sample volume collected should be 100 mls. If a participant cannot void 100 ml at once, it is permissible to store the sample in the refrigerator and to ask them to void again. The volume from the second void can be combined with the first sample. If fluid intake is not restricted, a participant should drink water. If the combined total volume is less than 100 ml, the available sample should be processed and sent to the lab.

If the sample is being collected prior to the GFR test, it must be collected before the Glofil injection is given. This sample should not be collected during the course of collecting urine for the I-GFR test. Please note that inability to provide this sample does not preclude a participant from continuation in the CRIC Study.

Midstream urine collection instructions-

For Males:

- Wash hands thoroughly.
- Cleanse the end of the penis with special towelettes beginning at the urethral opening and working away from it.
- Repeat the above procedure using two successive towelettes.
- Void into toilet for a few seconds and then stop. Restart urine stream and collect in sterile container.
- Void the remainder of urine into the toilet.
- Cap and avoid touching inside of container. Cover the container with the sterile lid touching only the outside surfaces of the lid and container.

For Females:

- Wash hands with soap and water
- Spread labia with 1 hand and hold apart for collection
- Use three special towelettes to clean area:
- Wipe down one side, front to back, with one towelette
- Wipe down other side, front to back, with second towelette
- Wipe down center, front to back, with last towelette
- Void into toilet for a few seconds and then stop. Restart urine stream and collect in sterile container.
- Void the remainder of urine into the toilet.
- Cap and avoid touching inside of container. Cover the container with the sterile lid, touching only the outside surfaces of the lid and container.

10.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 3000 ml collection container with the patient's initials.

Urine Aliquot Labeling

For the aliquot tubes, 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.

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 are provided to the participant at the Screening Visit. Written instructions are also provided.

IMPORTANT NOTE:

A 24 hour urine sample is considered inadequate if the total volume is less than 500 mls, or if the total collection time is less than 22 hours or more than 26 hours.

If during completion of the Specimen Collection [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. Save the original specimen in the event the participant is unable to provide a repeat specimen.

Participants who reach ESRD (dialysis and transplant patients) should continue to collect a 24 hour urine sample annually. However, the 500 cc minimum volume does not apply to these patients.

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°C or -80°C in a plastic rack or cardboard freezer box in an upright position.
- Store the third aliquot at 4°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.

Packaging Instructions for Specimens at 4°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.

Packaging Instructions for Specimens at -20°C or -80°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.

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.

Shipping Instructions

- Tubes stored at 4⁰C
- 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 -20⁰C or -80⁰C
- 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.D.2. Sample Processing for Urine Proteomics

Instruct each participant to collect a midstream urine sample in a urine specimen collection container. This specimen should be collected following the “clean-catch” instructions. The sample collected should be a minimum of 50 mL.

- Pour spot urine collection into the two 50ml conical vials and centrifuge at 2400rpm for 20 minutes
- Using a pipet, transfer the supernatants to the 10 aliquot tubes provided. Fill each tube to the 9mL mark. Be careful not to disrupt any cellular debris at the bottom of the tube. Any remaining urine can be discarded.
- For minimum urine collection, at least 50mL must be obtained. Then fill six of the ten 10 mL cryovials to the 9mL mark.
- Store the samples in the upright position. Immediately freeze the tubes at -80 C (if -80 C is not available freeze at -20 C).

10.D.3. Shipping Urine Proteomics Samples

- Ship samples to the central lab on dry ice on a monthly basis, according to a pre-arranged schedule with the Central Lab, with all of the other TRANS DRY samples
- Always ship on dry ice using the Packaging Instructions for Specimens at -20 C or -80
- Notify the Central Lab of Shipment by faxing the PROTRAN form to Fax: 215/573-8606

10.E. Collection, Processing, and Shipping of Blood Samples

Participants may find it more comfortable to have the 130 cc blood sample collected over more than one blood draw. For example, during the baseline visit, you may collect only the first seven tubes of blood and collect the rest of the specimen during the GFR test visit shortly thereafter. This is acceptable provided the time span is not more than three months.

- If a participant is known to have a low hemoglobin, the investigator may choose to defer enrollment or draw baseline blood samples during two separate visits.
- If a problem arises with the blood draw, it may be best to try to collect the blood samples later in the same visit or during an additional visit if the participant is willing. The minimum blood draw amount is 85 cc which includes the following:
 - One 10mL Serum Red top tube wrapped in aluminum foil (BD# 366441)
 - Two 10mL SST red/gray top tubes (BD# 366510)
 - One 5mL Na Citrate (0.105M) blue top tube (BD# 366415)
 - Two 5mL EDTA lavender top tubes (BD# 366452)
 - Three 10mL EDTA lavender top tubes (BD# 366457)

Equipment and Supplies

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

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.

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

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.

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 $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$.
- Check the refrigerator temperature ($4^{\circ}\text{C} \pm 2^{\circ}\text{C}$).
- Check the freezer temperature (either $-20^{\circ}\text{C} \pm 10^{\circ}\text{C}$, or $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$).

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.

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.

At participant arrival:

- Check that the ID number on each tube matches the participant ID.
- Check that the aliquot tubes are prepared and labeled.

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 should briefly describe the procedure:

“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.”

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."

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.

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.

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.

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.

Perform venipuncture.

- Grasp the participant's arm firmly, using your thumb to draw the skin taut. This anchors the vein. The thumb should be 1 or 2 inches (2.3 or 5.0 cm) below the venipuncture site.
- With the needle bevel upward, enter the vein in a smooth continuous motion.
- Make sure the participant's arm is in a flat or downward position while maintaining the tube below the site when the needle is in the vein. It may be helpful to have the participant make a fist with the opposite hand and place it under the elbow for support.

- Grasp the flange of the needle holder and push the tube forward until the butt end of the needle punctures the stopper, exposing the full lumen of the needle.
- Start a timer to measure the flow rate of blood into the first blood collection tube. If the flow rate in the tube is so slow that blood does not fill the first collection tube within 50 seconds, stop the blood collection and repeat on the other arm. If blood is flowing freely, the butterfly tubing can be anchored to the participant's arm using medical tape for the duration of the draw.
- Remove the tourniquet after blood is flowing into the second tube.
- Keep a constant, slight forward pressure (in the direction of the needle) on the end of the tube. This prevents release of the shutoff valve and stopping of blood flow. Do not vary pressure nor reintroduce pressure after completion of the draw.
- Fill each vacutainer tube as completely as possible; i.e., until the vacuum is exhausted and blood flow ceases. If a vacutainer tube fills only partially, remove the vacutainer and attach another one without removing needle from vein.
- When the blood flow ceases, remove the tube from the holder. The shutoff valve recovers the point, stopping blood flow until the next tube is inserted.
- EDTA tubes and NaCitate 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.

Blood Mixing During Venipuncture

- Only invert tubes containing anticoagulant such as EDTA (purple top) and NaCitate (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!!

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.

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.

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

10.F.1. 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 4°C

Freezer at -20 or -80°C

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.2. 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 10°C, 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.

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 labeled 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.

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 -20°C or -80°C 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 4°C 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 -20°C or -80°C on site.
- Two 5mL EDTA (purple top) tubes:
 - Affix label to one tube for HbA1C and refrigerate at 4°C 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 -20°C or -80°C on site
 - Affix labels to the other 5 tubes and refrigerate at 4°C 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.3. Packaging Instructions for Specimens at 4°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 – Dry Ice [TRANSDRY] 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.

10.F.4. Packaging Instructions for Specimens at -20°C or -80°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.

10.F.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.

10.F.6. Shipping Instructions

Tubes stored at 4⁰C

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 -20⁰C or -80⁰C

- 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 2ml cryogenic vial
- 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:

2mL cryovials same as those used in blood storage

Mfr# 5000-1020

Fisher Cat# 03-337-74

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 with other refrigerated blood and urine samples.

10.G.3. Packaging Instructions

- Place sample vials in a plastic Ziploc bag, sealed 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 -20°C or -80°C	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 one 12x75 polypropylene tube	Transfer serum into one aliquot	Refrigerate sample at 4°C	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 one 12x75 polypropylene tube	Transfer serum into one aliquot	Refrigerate sample at 4°C	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 one 12x75 polypropylene tube	Transfer serum into one aliquot	Refrigerate sample at 4°C	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 -20°C or -80°C	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 -20°C or -80°C	Ship to Central Lab once per month
Tube 7	5mL EDTA (purple top)	Affix label for HbA1C**	Refrigerate at 4°C	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 4°C	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 -20°C or -80°C	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 -20°C or -80°C	Ship to Central Lab once per month
Tube 11	10mL EDTA (purple top)	Affix label to collection tube	Refrigerate sample at 4°C	Ship to Central Lab within 72 hours			
Tube 12	10mL EDTA (purple top)	Affix label to collection tube	Refrigerate sample at 4°C	Ship to Central Lab within 72 hours			
Tube 13	10mL EDTA (purple top)	Affix label to collection tube	Refrigerate sample at 4°C	Ship to Central Lab within 72 hours			
Tube 14	10mL EDTA (purple top)	Affix label to collection tube	Refrigerate sample at 4°C	Ship to Central Lab within 72 hours			
Tube 15	10mL EDTA (purple top)	Affix label to collection tube	Refrigerate sample at 4°C	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
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Nail Clipping Collection

Nalgene cryogenic vials Mfr # 5000-1020	Fisher Cat# 03-337-7Y
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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. Lab Transfer Schedule

10.I.1. Daily Shipping Schedule

Specimens should be shipped to the CRIC Central Laboratory as soon as possible after they have been acquired. It is preferred that this occur within 24 hours of collection. It is permissible to store specimens at the clinical site for up to 72 hours provided they are stored under the following conditions:

Specimens should not be shipped to the CRIC Central Laboratory on Friday because they will not be received and stored properly and may be ruined. Specimens collected on Friday should be stored at the clinical site as described above and sent to the Lab on Monday for receipt on Tuesday.

10.I.2. 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

Month	Mon	Tues	Wed	Thurs	Fri
Week 1	Hopkins & MD				
Week 2	Penn		Cleveland (3)		
Week 3	Michigan (3)		Chicago		
Week 4	Tulane		Kaiser & UCSF		

11. Appendix C: ECG Manual of Procedures

12. Appendix D: GFR Manual of Procedures

12.A. Introduction – Glomerular Filtration Rate (GFR)

The GFR test is a method that accurately determines the level of glomerular filtration in subjects with renal insufficiency. This method of measuring kidney function is independent of changes in lean body mass or changes in protein intake. This test is performed by administering a subcutaneous injection of the GFR marker, Glofil (^{125}I -iothalamate), and measuring the urinary clearance of the GFR marker.

12.A.1. Patient Education

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 the testing aims.

- 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
- PRESENT THE APPROPRIATE MESSAGE
 - ◆ Test explanations should be tailored to each patient's ability to understand the material and to their individual needs.
- 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.A.2. Overview of Procedure

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.

The procedure is conducted as follows:

Prior to glofil injection:

Provide Patient Education	See Patient Education
Determine eligibility	See Eligibility Criteria
Administer Urine Pregnancy test, if appropriate	See GFR Test Procedure
Begin Patient Hydration	See Patient Hydration
Insert peripheral IV	See GFR Testing Phlebotomy Techniques
Collect background blood sample	
Collect background urine	See Urine Collection Procedure
Administer SSKI	See Thyroid Blockage with Super Saturated Potassium Iodide

Glofil injection:

Bladder is emptied	
Glofil injected subcutaneously in the upper arm.	See Radiation Safety Considerations for GFR

After glofil injection:

Some time is allowed to pass to allow the glofil to distribute throughout the body. This should be at least one hour and the participant should produce at least 250mL of urine to reflect a sufficient amount of distribution of the glofil dose.

T0: After one hour AND after 250mL of urine are produced from the time of glofil injection, collect 5mL of blood. This blood specimen is labeled as T0. No urine is saved at this time.

Begin collection of urine #1 - #4 and blood #1 - #4

From this point forward, urine and blood samples collected are necessary for calculating the GFR values. After at least every 30 minutes, participants will empty their bladder and provide a blood sample.

Each of these samples will be measured against the background samples of urine and blood, and the blood sample at T 0.

A GFR is calculated from each of these four samples and an average GFR value is calculated.

12.B. 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 are included on the GFR worksheet.

12.B.1. Materials and Equipment

- 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 (1mL increments) 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 (See next section)
- 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).

12.B.2. Ordering Glofil

Glofil (Sodium Iothalamate I-125 Injection) is a sterile, nonpyrogenic aqueous solution for injection. To correct for physical decay of this radionuclide, it must be ordered and used within a defined period of time. The following guidelines will ensure the appropriate use and dose of Glofil for GFR testing.

- Schedule GFR tests at least one (1) week after determining eligibility in the Assignment module and selection to the GFR subcohort. This will allow sufficient time to contact the SDCC and order a unit dose of Glofil.
- Provide as much advance notice as possible to the DCC when ordering Glofil for scheduled tests. This will reduce problems associated with ordering and shipping delays.
- Consider internal transfers that occur at the site when ordering, and allow sufficient time for the dose to reach its' destination. For example, if Glofil is received in Nuclear Medicine but is transferred to another building or department (GCRC, Radiology) for administration, allow time for this to occur.
- Provide the following information when submitting a Glofil order. Requests cannot be processed without this information.
 - ◆ GFR test date (this is essential information)
 - ◆ CRIC ID number and initials
- Send requests for Glofil to Jennifer Dickson at the SDCC.
dicksonj@mail.med.upenn.edu Phone: 215 – 573 -5569
- When delivery has been made to the Nuclear Medicine Department, you will be informed as soon as possible.

Delivery procedures such as wipe test, storage, and documentation of delivery of Glofil, varies among sites but must meet the requirements of each institutions Environmental Health and Radiation Safety guidelines. Likewise the documentation for injecting, handling, disposal, and cleanup of Glofil must meet all institutional and federal radiation safety guidelines.

IMPORTANT NOTE: A unit dose of Glofil can be used + / - 7 days of the labeled date. During this time frame the product is well within the acceptable radioactivity level and can be used to conduct a GFR test without compromising the test quality.

Example: If a unit dose of Glofil is dated 5/10/06, it can be used only between 5/4/06 and 5/16/06, inclusive.

- Each dose of Glofil has an **expiration date** after which it cannot be used, regardless of the range stated above. This expiration date is on the label.

12.B.3. GFR Test Procedure

- Determine eligibility prior to initiating the GFR test.
- 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. 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.
- 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.
- Women of childbearing potential (post-pubertal, premenopausal, and not surgically sterilized) must have a urine pregnancy test, within 72 hours prior to the GFR. 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.
- If the patient has had a radionuclide diagnostic test in the past month, using an isotope other than 99Technetium or 125I, the GFR must be rescheduled. The most common example of such a test is a thallium stress test.
- If the patient is on dialysis or has had a kidney transplant, they will not receive the GFR test.

Prior to Glofil injection:

- 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.
- Record the patient's height (cm) and weight (kg).
- 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 ¹²⁵I. This protects the patient and eliminates error in the GFR determination due to the additional elimination route for the isotope).
- Start hydrating the patient. A water load of 10 ml/kg is required during the next 90 minutes.
- 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 leurock adapter (Becton-Dickinson cat. no. 367290). The 6-inch line allows free motion for tube changes.

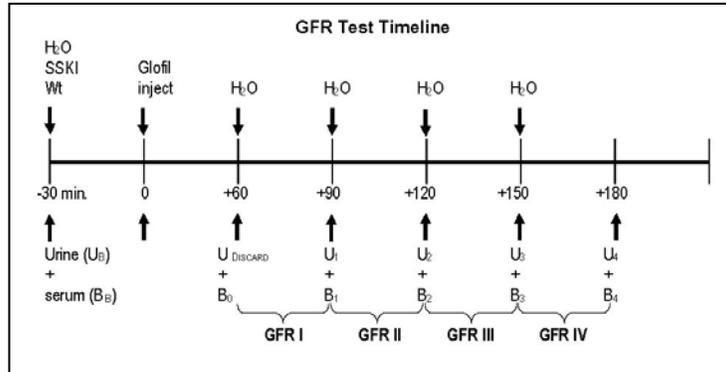
- Insert the I.V. catheter into the vein. Draw all the biochemistry samples and the GFR baseline sample. Immediately after obtaining the samples, heparinize the site with at least *one ml* of 100 u/ml heparin (or saline). If the participant is allergic to heparin, normal saline may be used instead. It is appropriate to use saline to flush the IV line if that is the policy of your institution.
- After flushing the line, 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.
- Collect background urine; record the time.

Glofil Injection:

- At least 30 minutes following the administration of the SSKI, the Glofil is injected subcutaneously in the upper arm. Record the time.
- Continue to hydrate the patient at the rate of 200-400 ml/hour as tolerated throughout the study.
- At least 60 minutes after the time of the Glofil injection, the patient should void. Record the time (time #0). Measure the urine volume. If this volume is at least 250 ml then continue with the test. 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.
- Once 60 minutes have elapsed AND the participant has produced at least 250mL, 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.

Begin collection of U#1- #4 and blood #1 - #4

- 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. Aliquot the urine. (If the flow rate for the period is low, extend the period to get additional urine and a higher flow rate, as described above). The flow rate for urines U-# 1 through U-#5 is required to be > 1.0 ml/min.
- Draw the next blood sample (S-#1). Re-heparinize the line. (The blood samples are not timed and should be drawn as close to the time of urine collection as possible. If you are unable to draw the blood sample within 5 minutes, set the urine aside first, draw the blood and return to aliquot the urine.)
- Repeat until four timed urines have been collected and appropriate blood samples drawn.
- 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.C. Patient Hydration

CRIC Hydration Procedure

- Water is usually used exclusively. If the participant cannot tolerate water, then gatorade, coffee, or non-protein drink may be substituted
 - ◆ Exception: pre-test light meal (< 10 grams protein) is permitted
- Defined hydration levels:
 - ◆ Before arrival for test: one quart (1000 ml) drunk the evening prior to the GFR test; and 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 (U_0): 10 ml/kg (700 ml/24 oz for a 70-kg patient)
 - ◆ For the remainder of the test following the first (U_0) urine collection: 200 to 400 ml/hour (equivalent to flow rate of 3.3-6.7 ml/min at equilibrium) or 1 to 2 – 8 ounce glasses/hour
- 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
- 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 before the GFR test visit and hydration on 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.D. GFR Testing Phlebotomy Techniques

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: Is there a single vein that must be protected at all costs, or are there several good sites?
- Desirable features of phlebotomy
 - ◆ free-flowing blood sampling
 - ◆ secure location
 - ◆ acceptable patient comfort

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 are 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 1cc of 100 units/ml flush. You may use a normal saline flush if the participant is allergic to heparin or it is the Hospital or Nursing Office policy to use saline-only flushes.

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

Phlebotomy Line Insertion And Blood Draws

- Use Universal Precautions
- Choose the largest appropriate vein, preferably in the antecubital 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, 1. 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

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 subcutaneous 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.E. Urine Collection Procedures

General Considerations

- collections:
 - ◆ background urine sample (i.e. before isotope injection); aliquot for gfr calculation
 - ◆ 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)

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 collections 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/aliquoting
 - ◆ measures to avoid collection "crossover" counts
 - ◆ proper labeling of samples

Patient Instruction For Urine Collections

- The first visit is the most important as this is the opportunity to teach the patient what must be done in preparation and during the test.
- At each visit, "reminders" should be repeated before each collection to 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 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)

Urine 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; This urine sample cannot be used. Discard this sample, but collect a blood sample and note the time. Next time use two Speci-pans placed "back-to-back" in bowl and collect for one additional period. (See below)
 - ◆ 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

Timing of Urine Collection

- 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.

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.

Avoiding 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 contamination:
 - ◆ proper aliquoting (see above)
 - ◆ thorough rinsing and drying of measuring containers before and after each collection

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.F. Thyroid "Blockage" With Super-Saturated Potassium Iodide

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 iodide (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.

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

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.

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.G. Radiation Safety Considerations for GFR

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.

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."

¹²⁵I-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

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
 - ◆ maximize 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 100cm²; upper limit of acceptable defined by RSO; monthly records
 - ◆ surface protection — absorbent paper: Choux, 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

(GFR) - Glomerular Filtration Rate

- 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 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**.

(GFRTRANS) – Specimen Transfer

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.

12.I. Processing and Shipping Samples

12.I.1. Preparing the Samples for Mailing to the Central GFR Lab

- When the blood samples have clotted, centrifuge the blood samples.
- Be sure to include the patient's name code and number on each of the pre-labeled tubes.
- 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).
- Place **three aliquots of each 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.)
- Tighten all the caps of the mailing tubes.
- Prepare the mailer for shipping with one frozen ice pack in the bottom of the inner Styrofoam box.
- 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.

- Place the zip-lock bag containing all the GFR samples into the inner Styrofoam box. Place the Styrofoam lid on the Styrofoam inner box.
- 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.
- 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
- 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.

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.

	Protein (g)
Breakfast Meal # 1	
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

Breakfast Meal # 2	
1 plain bagel (3 inch diam.) <u>or</u> 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 less than 10 grams 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
1/2 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	
1/2 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	
1/2 cup pasta, plain (e.g. spaghetti, macaroni)	3.36
1/2 cup spaghetti sauce	2.24
Salad:	
1/2 cup lettuce,	
1/2 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
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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.

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.

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.

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.

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.

13.C. DHQ Quality Control Procedures

- It is important to review the entire DHQ form thoroughly for missing responses and questions that have more than one answer. These errors may result in report errors that may not be detectable.
- The pages of the form should not be stapled or torn. Pages that are ripped in any way should be photocopied prior to transfer to the SDCC. Torn pages cannot be scanned.
- The four black boxes in the corners of the first page cannot be obscured with a staple or label. This causes scanning errors.
- The first page of the DHQ must be completed with the following information: complete header info, today's date, month and year born, gender. DHQ facesheets that do not contain this information will be faxed to the clinical center for clarification prior to being scanned into the data management system.

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14. Appendix F: ECHO Procedures

**CHRONIC RENAL INSUFFICIENCY
COHORT (CRIC) STUDY**

**HANDBOOK FOR ECHOCARDIOGRAPHIC
IMAGING AND DOPPLER
DATA ACQUISITION**

Version 1.1

Dated 5/20/2004

**Center for Quantitative Echocardiography
University of Pennsylvania School of Medicine
Philadelphia, PA
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Martin G. Keane, M.D., FACC, FAHA**

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Background

The Chronic Renal Insufficiency Cohort (CRIC) study was established in 2001 in order to gain an understanding of the relationship between progressive renal disease and cardiovascular disease. Chronic renal insufficiency (CRI) is a silent epidemic, affecting more than 10 million Americans. Patients with CRI suffer high morbidity and mortality not only due to progression to end-stage renal disease (ESRD) and dialysis, but also due to disproportionately high risk of cardiovascular morbidity and mortality in these patients.

The primary goal of the CRIC study is to examine the risk factors for cardiovascular disease among patients with varying degrees of CRI. Echocardiographic characterization of the ventricles and valves in terms of structure and function is an integral and important part of the risk evaluation of CRI patients, who are being recruited from seven clinical centers across the United States (including your own).

Echocardiograms will be performed in all patients at one year after enrollment and at follow-up of 4 years. You and your echo center are a crucial part of this step, and we are indebted to you for your efforts. We look forward to working closely with you over the next several years. Once performed, echocardiograms will be sent to the core echocardiographic laboratory at the University of Pennsylvania. It is at the core lab that a clinical reading of the echocardiogram will occur. The taped images will be quantitated in detail at the core lab as well.

Specific Aims

The goals of Doppler echocardiography in this prospective cohort study of chronic renal insufficiency (CRI) are:

- To characterize structural and functional cardiac disease in a large population with CRI, including LV myocardial mass and cavity size, regional and global systolic function, diastolic function, valvular function and pulmonary artery pressure.
- To assess changes in these parameters over time, to establish the pattern and rate of disease progression.
- To relate characteristics of left ventricular and valvular structure prospectively to the incidence of long-term adverse cardiovascular events.
- To examine the relationship of these cardiac structures and functional abnormalities to co-existent clinical risk factors and neurohormonal abnormalities in participants with CRI.

Optimal Doppler-Echocardiographic Imaging

To facilitate the efficient and accurate quantitative analysis of the imaging and Doppler velocity signals to be obtained in this study, participating technologists are requested to observe the following guidelines:

A good quality electrocardiographic signal should be obtained and recorded with all echocardiographic images and Doppler velocity signals.

SVHS tapes are the preferred format but digital echocardiographic images recorded on compact discs (CD-R) with Dicom format data are also acceptable. Keep a copy of the study and send the original to the core lab.

Record generously. Fifteen to twenty cycles of each 2-D and Doppler signal should be recorded.

Extra 2-D gain is indicated for quantitative analysis of two-dimensional images. It is preferable to overgain rather than to undergain. Harmonic imaging is generally not helpful as it can cause shadowing in the periphery of the image. If it must be used, please adjust the gain setting carefully to compensate.

Adjust the depth for the apical images to include the entire left atrium and maintain the same depth setting for all apical images and Doppler signals that are required by the protocol. Do not change the depth needlessly. Do not narrow the sector angle for two-dimensional imaging because this crops the LV images.

In apical imaging planes the maximum cavity lengths must be displayed and should be the same in all apical images.

Maximize the size of the pulsed and continuous Doppler spectral velocity tracings by adjusting the scale and using the baseline shift function. Optimize the reject and gain to provide thin spectral envelopes. Minimal gain should be employed. As the spectral Doppler will be used to provide information on the timing of intracardiac events, record all Doppler spectral velocity signals at sweep speeds of 100 mm./sec. Use of excessive wall filter should be avoided.

Optimize the color Doppler frame rate by narrowing the color sample box.

The continuous wave signal of tricuspid regurgitation should be sought from the parasternal, apical and subcostal imaging windows. The highest velocity waveforms will be analyzed.

All measurements will be made at the core laboratory.

The core laboratory at the Center for Quantitative Echocardiography at the Hospital of the University of Pennsylvania will monitor studies for quality and completeness and notify the participating centers and the SDCC of any deficiencies by fax.

SVHS Videotapes, tape labels and preprinted FedEx mailers will be purchased by individual clinical centers. Contact your Echocardiography Center for a recommended vendor of Super VHS tapes.

Data Acquisition – Echo Protocol

Two-dimensional Doppler/echocardiograms will be recorded at the 12 Month Clinic Visit and at the 48 Month Clinic Visit.

Echocardiographic examinations performed for this study should include but need not be limited to the following:

Parasternal Long Axis View: The long axis (LAX) image is optimized so that the interventricular septum is horizontal on the screen with the apex at the left. If the IVS angles up toward to the left, then a higher intercostal space should be sought. Moving the transducer closer to the sternum and turning the patient to a more lateral position will also help to display the IVS horizontally. Color Doppler interrogation of the left atrium for mitral regurgitation and left ventricular outflow tract for aortic regurgitation is performed. The two-dimensional image of the left ventricular outflow tract is magnified (zoomed) and recorded.

Parasternal Short Axis View: Ten to fifteen cycles of the short axis of the left ventricle at the chordal level should be recorded. In short axis the left ventricle should be round and the papillary muscles symmetrically disposed. The gain controls are adjusted so that there is no drop out from myocardial or endocardial echoes when the image is frozen. As the images are analyzed in stop-

frame, extra gain is required. A short axis of the base of the heart is then obtained and the aortic valve is recorded. The RV outflow tract is examined with color Doppler for the presence of pulmonary insufficiency.

LV M-mode: A standard M-mode of the aorta and left atrium and the left ventricle at the level of the chordae tendinae should be obtained from either the optimized parasternal long axis view or the parasternal short axis view.

Right Ventricular Inflow Tract: A careful color Doppler assessment of tricuspid regurgitation (TR) is performed. If the color signal of TR is identified, continuous wave Doppler is recorded at 100 mm/sec. sweep speed.

Apical 4 Chamber View: Two-dimensional echo images are recorded of the LV. The full length of the LV and the entire left atrium should be displayed.

Pulsed wave Doppler of the LV inflow tract should be recorded with the sample volume at the leaflet tips and not at the annulus.

The Doppler pulsed wave sample volume is then repositioned to obtain the signals from the LV inflow and outflow simultaneously for the measurement of isovolumic relaxation and contraction times.

Color flow Doppler of tricuspid and mitral regurgitant flows, if any, are obtained, and the continuous wave Doppler signal of tricuspid regurgitation is recorded at a sweep speed of 100 mm./sec.

Color M-Mode: The patient will be positioned in the left lateral decubitus position for the baseline echocardiographic measurements of the CRIC protocol. The color Doppler map of the mitral inflow will be acquired in the apical four-chamber view. Following optimization of gains and Nyquist settings (aliasing limit ~50-60 cm/sec), the M-mode cursor will be positioned parallel to the direction of the inflow jet. Color M-mode will then be obtained at a sweep speed of 100 mm/sec. A minimum of 10 consecutive cardiac cycles with identical gains and scale will be recorded on tape.

Pulmonary Vein Flow: Also in the apical four chamber view, the right upper pulmonary vein will be identified via 2D and color Doppler techniques. A Doppler sample volume will be placed into the body of the pulmonary vein. A pulse wave Doppler measurement of systolic and diastolic pulmonary vein flow will be made, with a sweep speed of 100 mm/sec. A minimum of 10 consecutive cardiac cycles with identical gains and scale will be recorded on tape.

Apical 5 Chamber View: The transducer is elevated slightly to show the LVOT. Color Doppler of the LV outflow is performed to assess aortic regurgitation. LV forward flow is assessed by pulsed wave Doppler with the sample volume approximately 0.5 cm. proximal to the aortic valve. Continuous wave Doppler is then used to obtain the maximum flow velocity spectrum through the aortic valve.

Apical 2 Chamber View: Two-dimensional echo images are recorded. Doppler color flow mapping of the left atrium is performed to assess mitral regurgitation.

Apical Long Axis View: Two-dimensional echo images are recorded. Doppler color flow mapping of the left atrium is again performed to assess mitral regurgitation.

Subcostal Views: If the parasternal LV short axis (SAX) views are not satisfactory the same information may be obtained from the subcostal SAX. TR color and CW Doppler can sometimes be obtained from this window. From a subcostal four chamber view the scan plane is angled to

the patient's right to image the inferior vena cava and this is recorded through several respiratory cycles.

Data Analysis

Measurements in the Core Lab

The following echo/Doppler parameters will be measured:

M-mode left ventricular dimensions at end-diastole and end-systole, the aortic root and left atrial diameters.

LV short axis cavity areas and cavity plus muscle areas from the parasternal short axis view.

LV end-diastolic and end-systolic lengths, areas, and volumes from the apical four chamber view.

Left atrial areas from the apical four chamber and two chamber views.

A sixteen segment wall motion score using the nomenclature recommended by the American Society of Echocardiography.

LV Doppler stroke volumes from the LVOT diameter and flow velocity integral.

Left ventricular diastolic function will be assessed using the pulsed wave Doppler signal of LV filling. Mitral valve E wave and A wave peak velocities and their ratio, and the E wave deceleration time will be assessed.

Left ventricular isovolumic relaxation and contraction times will be measured directly from the signal obtained by placing the pulsed wave sample volume between the LV inflow and outflow tracts. Left ventricular ejection time and diastolic filling time will also be measured. The peak velocity of the tricuspid regurgitation signal from continuous wave Doppler will be used to estimate pulmonary artery pressure from multiple imaging windows.

The IVC diameter will be visualized through several respiratory cycles for an estimate of RA pressure.

Valvular regurgitation will be assessed and semi-quantified with color flow Doppler for all four valves. In addition, the maximum spatial extent of the color signal of mitral regurgitant flow will be planimetered in two apical views.

Calculations

Left ventricular mass and geometry

Relative wall thickness will be calculated as the ratio of twice the posterior wall thickness divided by the left ventricular internal diameter in diastole

Left ventricular mass will be calculated from two dimensional images using the 5/6 area* length algorithm.

Left ventricular shape will be assessed as the ratio of short axis to apical four chamber cavity areas and as the ratio of LV cavity volume to the volume of a hypothetical sphere whose diameter is equal to the LV cavity length.

Left Ventricular Systolic function

- LV endocardial borders of apical four chamber images will be digitized at end-diastole and end-systole to obtain LV volumes and ejection fraction. Ejection fraction will be calculated as the stroke volume divided by end-diastolic volume multiplied by 100% ($EDV-ESV/EDV \times 100\%$). Left ventricular volumes will be calculated using the modified Simpson's rule method.
- The percentage change from diastole to systole in left ventricular diameter from the M-mode will also be calculated.
- Left ventricular wall motion will be scored using a standard sixteen segment model as recommended by the American Society of Echocardiography.

Left Ventricular Diastolic Function

- Left ventricular diastolic function will be assessed by the E wave deceleration time and by the ratio of peak early filling velocity (E wave) to the peak velocity caused by atrial contraction (A wave).
- Isovolumic relaxation time (the difference in time from the end of the Doppler flow velocity signal in the left ventricular outflow and the onset of Doppler transmitral flow) will be measured. Isovolumic contraction time, diastolic filling time and LV ejection time will also be measured. These will allow the calculation of the Tei index.

Valvular function and pulmonary artery pressure

- Valvular regurgitation will be assessed semiquantitatively for all valves from multiple imaging projections using color flow Doppler. The maximum spatial extent of the color signal of MR will be planimeted in two apical views.
- The peak difference between right ventricular and right atrial pressure will be assessed from the continuous wave signal of tricuspid regurgitation. Right atrial pressure will be estimated by visual inspection of the inferior vena caval diameter through several respiratory cycles. This will be added to the right atrial/right ventricular pressure gradient obtained from the tricuspid regurgitation velocity to yield the pulmonary artery systolic pressure.

Advanced Echocardiographic Diastolic Assessments: Color M-Mode and Pulmonary Vein Flow

- *Color M-mode*: Recorded color M-mode will be utilized to define the propagation velocity (V_p) of early inflow, per the technique of Garcia, et al ¹⁵². The slope of the first aliasing velocity is measured at a point ≤ 4 cm distal to the mitral valve leaflets. If the aliasing velocity is < 55 cm/sec, then V_p will be measured as the slope of the first color velocity after the mitral valve opening. Propagation velocity will be expressed as cm/seconds, but will also be indexed to body surface area.
- *Pulmonary Vein Flow*: Diastolic and systolic components of pulmonary vein flow will be quantitated from recorded Doppler images from the right upper pulmonary vein. These will be expressed quantitatively as velocity-time integrals (cm). The end-diastolic retrograde wave duration will be quantified in milliseconds. The systolic/diastolic ratio will be calculated as the mean value across 3 consecutive cardiac cycles.

Procedural Information

Schedule

Echocardiograms are performed on all CRIC Study participants at the 12 Month Clinic Visit and at the 48 Month Clinic Visit. It is not necessary for the Echo test to coincide with the clinic visit but it should occur within the visit window which is 2 months before and 2 months after the anniversary date.

Training

Echocardiograms conducted for the CRIC Study should be performed by an experienced or senior technologist. It is preferred that the lead technologist at the center acquires the study images and instructs other center technologists about the CRIC Study procedures.

The instructions provided in this manual should guide the technologist in the procedure. A training teleconference will be scheduled with all technologists who will perform echocardiograms in the CRIC Study. Subsequent teleconferences may be conducted as needed in order to address study or site specific issues and questions. The Center for Quantitative Echocardiography at the University of Pennsylvania will provide fax feedback to sites for initial Quality Control assessments. Personnel from the Center for Quantitative Echocardiography are available Monday through Friday from 8 AM – 4 PM [Eastern] via telephone and email to assist in technical matters.

Ted Plappert
Phone: 215-349-5753
Fax: 215-349-8444
Pager: 610-734-6760
E mail plappert@uphs.upenn.edu

Procedure

Complete the ECHO CRF with all of the CRIC identifying information. A copy of this CRF will accompany the original videotape of the test.

Perform the Echocardiogram as described in the protocol above.

Assess the images for the alerts listed on the CRF. Notify the CRIC site coordinator and the SDCC of the occurrence of an alert by faxing the CRF as soon as possible to the numbers indicated on the contact sheet. This review must occur within 24 hours of acquisition of the echo.

Label the videotape with the following information:

- CRIC ID #
- Center and Site number
- Participant initials
- Date of test

Copy the videotape or produce a CD of the stored images and label copies as described above. According to HIPAA regulations, images transferred from the clinical site to the Center for Quantitative Echocardiography must be de-identified of participant protected health information (PHI) such as name or Date of Birth (DOB).

Send tapes on a **weekly** basis to the address below using traceable courier service. Complete the Echocardiogram Transfer form to indicate the studies that are being shipped to the Center for Quantitative Echocardiography.

Send the **original** videotape to:

Ted Plappert
Center for Quantitative Echocardiography
Rhoads Building, Ground Floor
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104

Quality Control

The initial set of five (5) echo tests conducted at each clinical site will be reviewed to assess the quality of the images. This information will be categorized within seven (7) views on the Echo Measurements form which is completed for each study by the Center for Quantitative Echocardiography. Images will be evaluated as poor, fair, good or not analyzable within the following views:

- M-mode
- 2-D parasternal
- 2-D apical
- LV inflow Doppler
- LVOT Doppler
- TR Doppler
- Color Doppler

This overall assessment will take the form of an Echo Image Quality Control Report for use by centers and the Steering Committee. Images that are evaluated as unacceptable or that demonstrate the need for additional instruction or attention to technique will be reviewed with the technologist who acquired the image. Personnel at the Center for Quantitative Echocardiography will continue to evaluate the images produced at a site until they are of acceptable quality.

The protocol will be reviewed in detail via telephone with the chief research technologist at the coordinating center. The first 5 studies of each center will be assessed for accuracy and quality by the coordinating center technologist, and remedial measures will be taken, if necessary. This may require selective site visits by the coordinating center technologist for hands-on training at the clinical center. Ongoing assessment for accuracy and quality will continue for all tapes analyzed at the core lab throughout the course of the study.

Intraobserver variability for both Vp and pulmonary vein flow measurements will be performed on 50 randomly selected cases. Measurements being performed by the same individual over 1 month apart will be reviewed in a blinded fashion. Interobserver variability will also be assessed in a similar fashion, with quantitation of 50 randomly selected cases by two or more investigators. Drs. Martin St. John Sutton and Martin G. Keane of the University of Pennsylvania echocardiographic core lab will supervise all quality control measures.

Videotape Label Template

Participant ID: ___ - ___ - _____	Participant Initials: ___ ___
Clinical Center: ___	Site: ___
ECHO Date: ___ / ___ / _____	

Data Forms

Echocardiogram [Echotech]

This form is completed by the Study Coordinator and/or Echo Technologist. Record the following information:

- Confirm that Echo was performed and the date.
- Record the measured height and weight from the corresponding PHYASSESS form.
- Measure recumbent blood pressure at the end of the study while the participant is in the supine position.
- Record the 4 digit Technician ID number. This is important for quality control monitoring.
- Check the Immediate Alert conditions during the test or within 24 hours of acquisition of the Echocardiogram. This is the responsibility of the Echo technician or reviewer.
- Provide COMPLETE contact information for the Echo technician, CRIC Study Coordinator and Investigator.

Echocardiogram – Transfer [Echotrans]

This form is completed by the Study Coordinator prior to shipment of Echo videotapes to the Center for Quantitative Echocardiography at the University of Pennsylvania. Upon receipt of study tapes, the lab will assign an independent tape number to them. The SDCC will independently confirm the tape transfer process.

Echocardiographic Measurements [Echomeasure]

This form is completed by the Center for Quantitative Echocardiography on review of the test. The results will be transferred to the SDCC on a monthly basis. The information contained on this report will be used for analysis and quality control assessment.

Echocardiogram Reports

The clinical interpretation of the Echocardiogram will be generated by the Center for Quantitative Echocardiography at the University of Pennsylvania. A copy of this report will be filed at the SDCC. These reports (identified by CRIC ID #) will be mailed to clinical sites. See Section IX for a sample report.

Contact Information

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Hospital of the University of Pennsylvania
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E-mail: suttonm@mail.med.upenn.edu

Sample Clinical Report



Echocardiographic Report

Hospital of the University of Pennsylvania

Martin St. John Sutton, FRCR
Director, Non-invasive Imaging

Patient:**Date:** 04/18/04**Age:****DOB:****Location:** HUP**Height:** 60 in**Tape #:** DIGITAL**Study:** Routine**Weight:** 172 lbs**BP:** 0/0**Technologist:****Referring:****History:**

4/08/04

Reason:**Dimensions:**

LA: The left atrium is normal.

LV: The left ventricle is normal in size with normal systolic function. The ejection fraction is 70%. The left ventricular filling pattern is normal.

AV: The aortic valve is normal and trileaflet.

MV: The mitral valve is normal. There is trace mitral regurgitation.

RA: The right atrium is normal.

RV: The right ventricle is mildly dilated with normal function.

PV/PA: The pulmonic valve is not well seen. There is physiologic pulmonic regurgitation. The pulmonary artery is normal.

TV: The tricuspid valve is normal. There is mild tricuspid regurgitation which is centrally directed. Normal PA pressure (PASP=24mmHg, RAP=14mmHg).

Pericardium: The pericardium is normal. There is a trivial circumferential pericardial effusion.

Aorta: The aorta is not well seen. The aortic root is normal.

IAS: The interatrial septum is normal.

IVC/SVC: The inferior vena cava is not well seen. The superior vena cava is not well seen.

Conclusion:

Study is diagnostic for the question posed. Patient terminated the current study. Normal LV size with normal systolic function. LV filling pattern is normal. Normal, trileaflet aortic valve. Normal mitral valve. There is trace mitral regurgitation. Mildly dilated RV with normal function, consistent with gravid state. There is mild tricuspid regurgitation. When compared with study images from 3/15/04, the LVEF is similar, the PASP has decreased by 12 mmHg. The trivial pericardial effusion is new. AR is not detected on the current study.

15. Appendix G: EBT Procedures

***RENAL INSUFFICIENCY COHORT
(CRIC) STUDY***

COMPUTED TOMOGRAPHY

MANUAL OF OPERATIONS

(a) Final Version 1.0

(b) April 28, 2004

EBT Reading Center
Matthew Budoff, M.D.
UCLA School of Medicine
Torrance, CA

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I. Background and Goals

EBT is a sensitive method to detect the presence, anatomical location, and extent of coronary calcification. Electron beam tomography to measure coronary artery calcification will be performed in one third of the CRIC Study participants after one year of follow-up and again at 4 years (in the same subcohort as those undergoing iothalamate GFR measurements). The introduction of Mechanical Multi-Slice Spiral (MSCT) Scanners with shorter rotation times presents additional options for cardiac imaging with conventional CT scanners. New MSCT scanners offer the possibility of high quality cardiac imaging with good reproducibility. In addition, thin slice scanning protocols [4 – 16 images] can improve the performance of these scanners.

The CRIC Study Steering Committee, in consultation with Matthew Budoff, MD, Division of Cardiology, Harbor-UCLA Medical Center, has decided that for the purposes of studies conducted within CRIC, EBT or MSCT may be used to assess coronary calcium. Dr. Budoff, who is collaborating with the CRIC Study as the Principal Investigator of the EBT Central Reading Center, has recommended that EBT or MSCT scanning can be conducted on CRIC Study participants. There will be no significant difference in information obtained from these different modalities.

II. Qualifications of Personnel

Field Center technologists should have appropriate knowledge of cross-sectional anatomy, physiology, and pathology related to the heart. Training sessions will be conducted via teleconference and individually as needed. Technologists must be certified as RTs in their state. It is recommended that technologists also have at least two years of experience in chest computed tomography. The technologist should also have a basic knowledge of cardiac CT, knowledge of computer software applications, data formatting, and experience with the workstations and data formatting / transmission procedures used.

To ensure quality control, each Field Center should have designated CT technicians who will perform the examinations. Each technologist involved in the study should also have a complete understanding of this protocol, be experienced at providing breath-holding instruction, ECG gating, operation of the EBCT.

For purposes of increased reliability and quality control, cardiac scans will be done twice on each subject.

III. Scanning Equipment and Centers

The scanners used will be:

CC	Site	NAME	SCANNER
01	01	University of Pennsylvania Medical Center	C-150
02	01	The John Hopkins University	EBT or Siemens S4+ Volume Zoom-Phantom-MESA
02	02	University of Maryland	[EBT at Hopkins]
03	02	University Hospitals of Cleveland	Siemens Sensation 16 - Phantom - EDIC
03	03	Metrohealth Medical Center	
03	04	Cleveland Clinical Foundation	
04	01	University of Michigan at Ann Arbor	GE-16
04	02	St. Johns Health System	
04	03	Wayne State University	
05	01	University of Illinois at Chicago	C-150
06	01	Tulane University Health Science Center	Imatron C-300
07	01	Kaiser Permanente of Northern California	EBT-C300
07	02	University of California, San Francisco	

IV. Reader Training and Site Certification

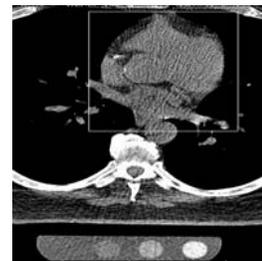
Prior to the start of the study, each site will send one sample case following the protocol to ensure understanding of the protocol. The first five cases will be carefully evaluated to ensure that they have been properly transmitted, are readable and are properly documented. Dr. Junichiro Takasu will read the CT exams. Dr. Takasu has read thousands of studies for research purposes, and will devote approximately 35% effort for reading these studies. He is recertified yearly by the director of the reading center. Dr. Budoff will evaluate the first 5 scans from each site (test cases) to ensure proper scanning and following of all protocols.

V. Participant Scheduling

Study Coordinators will be responsible for scheduling CRIC Study Subcohort participants for EBT tests to coincide with the 12 month and 48 month follow-up clinic visits. It is not essential that this test occur on the same day as the annual clinic visit but should occur within the visit window which is two months before and two months after the anniversary date.

VI. Scanning Table and Calibration Phantom.

A special gel stuffed mat will be provided with the calibration pad phantom to prevent artifacts and for subject comfort. This pad is placed between the phantom and the patient. The calibration phantom will be placed inside the blue catcher bag with its long axis parallel to the long axis of the scanning table. The phantom is made of tissue equivalent plastic with rods of hydroxyapatite of known radiographic density. The technologist will position the subject so that the length of the phantom covers the expected length of the heart. The phantom will be the one pictured on the right.



VII. Scanning Procedure

The scanning procedure described below, consisting of two scans done in succession on each subject, will require approximately 20 minutes of the subject's time. Minimal respiratory motion and maximum accuracy and reproducibility require this duration. In unusual cases, this may require as many as 30 minutes. In many cases, the procedure will be completed in 15 minutes or less.

Entering the ID

This very important step must be done correctly to prevent any irretrievable loss of CT data. All necessary information must be entered into the scanner system, including your technician ID number, Clinical center and site identification. The CRIC study patient ID number must be placed in the ID Field, and participant initials will be placed in the name field.

CRIC ID: 07022345

Center # 07

Site # 02

The time stamp on each CT record will determine whether the scan is the first or second in the sequence of two scans.

Preparation of the Subject (3 minutes)

Subjects weighing more than 300 pounds will not be scanned due to technical difficulties. For the purpose of making this evaluation, participant self report is considered reliable information. The technologist will ask women if they might be pregnant and will not scan them if they answer affirmatively. The technologist will attach three electrocardiographic electrodes under the left clavicle and on either side of the thorax near the axillae (to maximize ECG signal).

Complete the **EBTTECH** Case Report Form. Include complete contact information for the EBT technician who performed the test as well as the study coordinator.

Breath Holding Instruction (3 minutes)

The technologist will instruct the subject on the importance of breath holding and immobility during scanning. Whenever possible, an interpreter will assist in the instruction of subjects, not fluent in English.

Checking the Scout Image (1 minute).

The technologist will instruct the subject to take three deep breaths, and then to hold his/her breath (at end-inspiration), while acquiring an 11 cm scout image, beginning 180 mm below the sternal notch. This will provide views of the chest on the image monitor at the operator console. From this, the technologist will check patient centering and choose the position for the highest scan (at the lower margin of the bifurcation of the main pulmonary artery). The couch will be moved to the start position. The technologist will check subject and phantom positioning in the scout image.

Default Scanner Settings. At least 10.5 cm of data in the z direction will be acquired with each scan and the scan Field of View will be 35 cm for all scanners (to incorporate the phantom in the image). For each scanner, the default settings will be as follows:

- Imatron EBCT scanners: 130 kVp, 630 mA, scan time 100 msec, 3mm collimation, sharp reconstruction filter. For EBCT scans, prospective cardiac gating will be used with scanner triggering at 50% of the electrocardiographic RR interval. The EBCT scanner table will scan after each table increment of 3 mm (sequential axial scans). The technologist will acquire 40 image slices to ensure that the entire heart is scanned.
- General Electric helical scanner will be set at (KV120, mAs variable according to local protocol for body habitus, 500 msec). Siemens scanners will be set at (140 kV, mAs according to local protocol, 500 ms). This dependence on heart rate is needed in order to provide gapless continuous volume coverage. The equation is: $\text{pitch} = 1.5 * (\text{BPM}/60)$. Note that we define the pitch as table feed per full rotation divided by the collimation of 1 slice.

TRIGGERING FOR GE and SIEMENS Scanners will be at 50% of the R-R interval, using prospective gating, with image acquisition scan time set at 100 to 300 msec, and matrix to 512. The technologist will set the image slice thickness to 3 mm and will acquire 40 slice images.

Reconstruction. The technologist will use the 35 cm field of view and the sharp reconstruction kernel for all EBCT scans. Standard kernel will be used for all spiral scans. The General Electric helical scan data are reconstructed using a segmented scan reconstruction algorithm on the scanner console immediately following the study. Spiral scanners will use a partial scan tube rotation (~240 degree) with optimized reconstruction techniques that provide 250 – 300 msec temporal resolution in the center area of the scan field of view.

Imaging (6 minutes).

All scanning will be done with a single breath hold. Though total imaging time will be approximately 30 to 40 seconds, double scanning will require about 5 to 7 minutes to complete. The technologist will first acquire one entire series of image slices. The technologist will instruct the subject to relax on the table while he/she reconstructs and assesses the adequacy of positioning, ECG gating and lack of respiratory motion. If these are adequate, the technologist will immediately acquire another series of image slices while the subject remains immobile and in an identical position. Once again, he will assess the adequacy of the images.

Radiation Dose Considerations

The total radiation dose during one set of scans is approximately 1400 mrem (skin dose) for EBT scanners used in this protocol, and 3000 mrem for spiral scanners (dual heart scanning). The following may be helpful for informing subjects and institutional review board regarding radiation exposure from this study.

DUAL HEART SCANS ONLY

Scanner	Skin Dose	Effective Dose	Background Effective
Imatron	1260 mrem	1.2 mSv	2.3 – 3.0 mSv
Siemens	1900 mrem	3.0 mSv	2.3 – 3.0 mSv
GE	1540 mrem	2.4 mSv	2.3 – 3.0 mSv

Cardiac Dose

The radiation dose during two sets of scans is approximately 1200 mSev (skin dose) for Electron Beam Computed tomography, 2,600 mSev for Siemens and General Electric Scanners used in this protocol. This will be applied to the thorax covering 12 cm in the z axis.

The following may be helpful for informing subjects and institutional review board regarding radiation exposure from this study. The recent study measured the actual radiation to the participant using the proposed protocols for Siemens and EBT. (Hidajat N, Wolf M, Rademaker J, Knowllmann FD, Oestmann JW, Felix R. Radiation Dose in CT of the Heart for Coronary Heart Disease and CT of the Lung for Pulmonary Embolism: Comparisons between single-slice Detector CT, Multi-Slice Detector CT and EBT. *Radiology* 2000;217:374). Similarly, Siemens recently published data that the current protocol for calcium scanning requires 1.4 mSev of radiation, as compared to 0.6 mSev for EBT. New protocols are being developed by Siemens to reduce this radiation dose for each scan to 1.6 mSev, but this 'pulsed' protocol is not yet widely available. If available prior to the start of the study, or during the study, this will be considered as a change to significantly reduce radiation exposure to the participants. The listed radiation dose is per scan, with two scans being suggested to ensure adequate data and reduce variability.

Current estimates of the risk of fatal cancer from ionizing radiation for the adult working population are .004% per mSv (effective dose) over a 20 year period (assuming linear extrapolation). Thus, the additional risk of developing cancer for a participant in CRI during the next twenty years is between 8 per 100,000 and 12 per 100,000 for each CT examination. Each EBCT examination adds the equivalent risk of one year of background ionizing radiation, each spiral CT adds the equivalent of three years of background ionizing radiation.¹

Identification, Storage and Transport of Image Data

The following will ensure proper scan identification and subject confidentiality. The technologist will record each volunteer's study id number in the medical record number field of each scan. The date and times of the two scans and the identity of the scanning site and technologist will be identified in the appropriate fields. The technologist will store images in retrievable format on optical disk (MODs). Images will be transferred to a local work station which has an INTERNET interface to be used for transfer to the reading center.

VIII. Scanner Quality Assurance

Regular Scanner Calibration to Water

It is strongly recommended that the technologist at each center check the scanner at least weekly using a standard water phantom. These will include zeroing and calibrating the scanner unit.

¹ International Commission on Radiological Protection. "1990 Recommendations of the International Commission on Radiological Protection", ICRP Publication 60, Ann ICRP 21(1-3), 1991.

CT Calibration Measurements for Quality Assurance [Twice Monthly]

Each clinical site will have a QCT calibration phantom (Image Analysis Inc) and a torso QA phantom (Image Analysis Inc) containing a central plug with a known concentration of hydroxyapatite (100mg/cc). The calibration pad contains cylindrical rods and will be contained inside of a recess in the table pad for patient comfort.

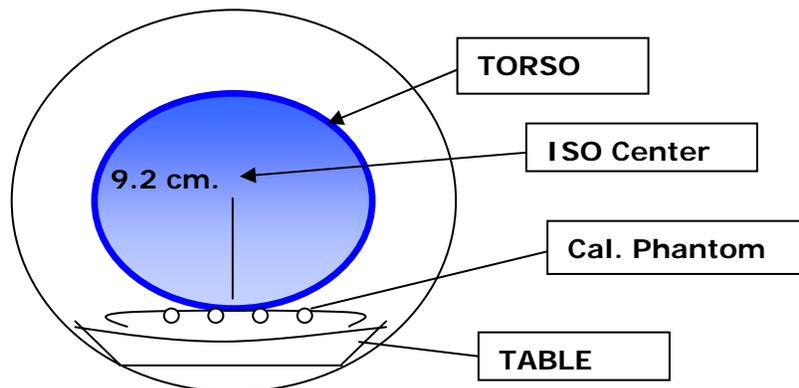
Quality assurance calibration measurements will be done weekly during the study initiation period. The initiation period will last until the site has been informed that 5 scans have been produced and transmitted satisfactorily. Quality assurance calibration measurements should then be done twice a month during the active scanning period of the study.

Every two weeks, quality assurance scans of the torso phantom allow convenient and quick verification of accuracy and precision of the CT scanners at different sites.

Complete the **EBTQA** form and fax it to the EBT Reading Center on a quarterly basis.

Positioning the Calibration and Torso Phantoms

Make the table height such that the center of the calibration phantom is located at a distance of 9.2 cm +/- 1.0 cm from isocenter of the scanner field of view. Place the torso phantom on top of the calibration phantom (positioned in couch pad) and using your laser alignment light, adjust the table height until the torso center insert is at the location of isocenter (on grid). This is the table height you will use for QA scans with your Torso phantom.



Scanning the TORSO QA Phantom

After the correct position has been determined, take a vertical axial slice through the center of the TORSO phantom. Use the same parameters as with patient exams. Reconstruction should be done with the same parameters as in scanning study subjects.

Display the axial image on the CT monitor and examine it to ensure that it is free of artifacts, such as air gaps and streaks. Ensure that the calibration phantom is included in the field of view. If there are significant artifacts over the calibration phantom, discard the image and rescan the phantom.

Using your CT software place ROI's on the calibration phantom reference samples (0, 50, 100, 200 mg/cc). The 0 sample will be an apparent blank space on one end of the calibration phantom. Place an ROI in the TORSO vertebral sample. The ROIs should be as large as practical while remaining completely within the reference cylinder. (We recommend ROIs about 70% of the sample area.) Record the five mean CT numbers within these five ROIs and send these numbers by FAX or E-mail to the CRIC Study reading center (Email, fax) using the **EBTQA** forms provided (See attached QA Data Sheet). Record the five mean CT numbers within these five ROIs.

File the data sheet for your records. Send these forms by FAX on a quarterly basis to the study reading center, attn Fred Flores (310-222-3841).

IX. Data Transmission of Studies

The technologist will transmit the studies to the local work stations if this has not been done during scanning. He/she will archive each study locally and leave a copy on the hard disk of the work station until it has been successfully transferred to the reading center. He/she will transmit the studies electronically using DICOM transfer on the local workstation to the reading center on a given afternoon of each week. He/she will simultaneously FAX the list of CRIC Study ID numbers transmitted at that time to the FAX number 310-222-3841 (ATTN: Fred Flores).

The CT Data Manager will check each study to ascertain if it has been completely received. If it has been so received, the study will be put on the queue to be read by the reader. If it has not been received, the data manager will immediately communicate the identity of the study to the field site technologist and request that another attempt be made to send that study. The CT data manager will enter the identity, scan date, scan time and date and time of transfer of each study into a running log, a copy of which will be sent weekly to the coordinating center.

The CT reader will backup studies onto CDs as they are read. The reader will label each disc with a volume name and the date the CD was created. The reader will print a directory to be stored with each CD. Each CD-R that is archived will thus have a printed list of its contents inserted into its sleeve. The Data Manager will back check the CDs to be sure that they contain complete studies.

X. Data Flow

A complex data flow diagram is contained in the Appendix. In brief, the following illustrates the principles of data flow:

Images. (Data manager: Ferdinand Flores (Phone: 310-222-8015) - Reader J. Takasu)

1. The scanning tech will FAX to the reading center (310-222-3841) a separate list of all subjects for whom an attempt is being made at INTERNET electronic transmission of images. This is FAXed on the FAX transmittal sheet in the appendix.
2. Simultaneous with this FAX, the scanning tech will attempt transmission of images for all subjects whose ID numbers are on the FAX list.
3. The reading center data manager will check the work station for the arrival and completeness of the images corresponding to the CRIC ID numbers on the FAXed list.
4. The data manager will log in study ID numbers on an electronic spreadsheet in EXCEL for all studies completely received. This is the spread sheet referred to above.
5. The data manager will print this spreadsheet as soon as it is complete and deliver it to the reading center director to begin the process of reading.
6. The reader will then read the coronary and aorta scan studies. Dr. Budoff will over-read approximately 20 % of the scans. The data manager will e-mail the spread sheet of studies actually received and loaded on the work station by the data manager, labeled with the date sent to the CRIC Data Coordinating Center (DCC) as soon as it is complete. The CRIC DCC will check the spread sheet from the reading center against the master list. On a weekly basis, the coordinating center will inform the Reading center data manager of missing studies.
7. The reading center data manager will track down the studies that have not been received by communicating with the scanning sites on a weekly basis.
8. The same procedure will be applied to studies which have not arrived.

Reading Results. (Data manager: Ferdinand Flores (Phone: 310-222-8015))

1. The readers will automatically accumulate results as they read in their results files called summary of scores.

2. The data manager will email these results to the coordinating center every Friday afternoon. The results file will be labeled with the readers initials and the date and time that it was electronically sent to the coordinating center.
3. The coordinating center will communicate to the data manager whenever expected results are incomplete or not received.

XI. Contact Information

FAX to EBT Reading Center: 310- 222 – 3841
Data Problems: Fred Flores (Phone) 310- 222-8015

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16. Appendix H: Out of Clinic (OOC) Visit Protocol

Definition: An out of clinic visit is any visit outside the CRIC clinic.
An out of clinic visit may be done at the participant's home or other health care facility with the participant's permission and/or health care facility. OOC visit must be rare and infrequent and may not be used regularly to take place of a clinic visit. Only standardized CRIC equipment MAY be used for the OOC visit.

The CRIC clinical site must check with their IRB and review their consent form to make sure that home visits are acceptable for data collection.

Purpose: The purpose of the OOC visit is to collect data in participants who are unable to attend the annual visit but agree to continue participation in the study.

The following general guidelines have been developed for out-of-clinic visits:

- ◆ Safety for the study participant as well as the staff is of utmost priority in the clinic's decision as to whether an OOC visit is appropriate for collection of data. **If there are questionable staff safety issues, DO NOT ATTEMPT A HOME VISIT.**
- ◆ Two staff members must attend the OOC visit.
- ◆ OOC visits may be completed for "lost-to-follow-up" participants to encourage them to return to the clinic for outcome measurements.
- ◆ Scheduled honorarium may be given to the participant at an OOC visit if study outcome measures are completed.
- ◆ The visit may be completed over 2 days, if needed.
- ◆ All guidelines regarding collection of outcome measures must be followed (such as fasting bloods).
- ◆ Only standardized CRIC equipment must be used for the OOC visit.
- ◆ Measurement procedures should be followed as done in the clinic, i.e. blood pressure should be done using the right arm, participant sitting for five minutes with back supported and feet flat, etc.
- ◆ Weight and blood pressure measurement "by report" is not acceptable as outcome data. Only measurements done by certified study staff will be acceptable outcome data. If unable to collect, data is considered missing and an incomplete visit form must be completed for missed outcome measures. For example, participant had weight measured at their last PCP visit, this weight would not be acceptable as "official CRIC weight" for research purposes.

Equipment & Supplies Needed for Out Of Clinic Visits

- Cooler with Cold packs
- Gloves
- Blue Chux
- Blood drawing supplies and vacutainers to collect annual samples (alcohol pads, 2 x 2 gauze, needles, tourniquet, bandaids, urine cup with screw-on lid to collect biohazard materials such as used needles, blood-stained alcohol pads, and 2x2 gauze). These items will need to be returned to the clinic for proper disposal in biohazard/sharps container. Follow your local IRB regulations concerning blood collection at home.
- Urine cup for urine collection.
- CRIC recommended portable scale and calibration weight. Recommended Portable scale (QC check needs to be done prior to leaving the clinic) Use form for scale QC check.
- Tycos handheld aneroid BP device with all cuff sizes

- Stethoscope and Doppler
- Tape Measure—to measure arm circumference.
- ECG Machine, ECG leads and all need supplies.
- BIA and needed supplies
- Nail clippers and container
- Data Collection Forms
- MMSE supplies
- Questionnaires
- Contact information update
- Updated consent form, if applicable
- Medical release forms, if applicable
- Pens, pencils, marker.
- Snacks (cheese or peanut butter crackers, orange juice, hard candy, etc) - in case of participant and/or staff hypoglycemic episode. Snacks should be stored in a separate lunch bag from the rest of the supplies.

The Data Collection Priorities are further broken down by the approved Priority of Data Collection for follow up visits as noted below:

Order of Priority of data collection during follow-up visits:

First Priority:

Updated Informed Consent, if applicable

Patient contact information (PT CONT)

Health care provide (HP CONT)

Blood pressure (BP CRF)

PHYS ASSESS (WT only) MedWeigh MS-3200 Digital High Capacity Scale/Bariatric Scale

Concomitant medications (CMED)

Medical events (EVENTS)

Medical history (MEDHX)

Draw blood in the following order:

1 RED GRAY TUBE (marble-top)

1-10 ml Red Top

2-10 ml Tiger Top

1-5ml Blue Top

1-5ml purple Top

2-10ml Purple Top]

Second priority (within this category, not arranged in order of priority):

24 hour urine

ECG

Pulse wave velocity baseline, yr 2 and yr 4

PHYS ASSESS---BIA/ABI, GIRTH, HT

PHYS ACT

KDQOL questionnaire

KCQ questionnaire

BDI-Beck Depression Inventory

Spot urine for proteomics

NSPEC-nails

DHQ-Diet questionnaire

Third Priority: Requires separate scheduling (within this category, not arranged in order of priority):

GFR-usually needs prior scheduling (if in sub cohort-done Yr 1 and Yr 4)

ECHO (if pt is Yr 1 and Yr 4)

MSCT or EBCT (if in sub cohort-done Yr 1 and Yr4)