CHRONIC RENAL INSUFFICIENCY COHORT (CRIC) STUDY

Protocol Amendment #3
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Introduction

This protocol amendment has been prepared by the Scientific and Data Coordinating Center (SDCC) at the University of Pennsylvania for the CRIC Study, sponsored by the NIDDK. As such, it will be distributed to the participating clinical centers for submission to their institutional IRB. The changes proposed in this document have been approved by the CRIC Study Principal Investigators and the Steering Committee.

The proposed changes described in this amendment refer to the approved CRIC Study Protocol, Version 2.0, dated, April 20, 2005. The following documents are included with this amendment:

1. CRIC Study Protocol, Version 2.0.

2. Revised Informed Consent Form, Version 3.0 – This revised informed consent form reflects the changes described in this amendment.

3. Appendix to Amendment #3 – The complete protocols and informed consent forms associated with the following ancillary studies are included:

    a. CRIC Plus Protocol and Informed Consent Form

    b. Retinopathy in Chronic Renal Insufficiency Cohort (RCRIC) Study Protocol and Informed Consent Form

    c. Cognitive Function in Chronic Renal Insufficiency Protocol and Informed Consent Form

    d. Sleep Disturbances as a Non-traditional Risk factor for CKD Protocol and Informed Consent Form

    e. Genetics of Atherosclerosis in Chronic kidney Disease Protocol and Informed Consent Form

CRIC STUDY PROPOSED AMENDMENT LISTING

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A. Schedule Variance

The CRIC Study enrolls participants with renal disease in a cohort, conducts tests and collects data on all members. Depending on date of enrollment, participants will be followed for up to five years. As part of this cohort study, one-third of eligible participants are selected to be in a sub-cohort and experience additional testing (GFR and cardiac CT/EBT) on a schedule described in the protocol. However, there are many reasons participants deviate from the testing schedule and those tests originally scheduled during the Baseline Visit (Visit #3) and annual follow up visits, are sometimes not completed according to the original schedule. Participants are willing to complete the study tests on a different schedule that is often later than the time frames described in the original protocol. This protocol deviation has been evaluated with the investigators and biostatisticians at the SDCC who have determined that this schedule variance can be accommodated, noting that the important factors are to collect data at two time points during study participation and to strive to maintain the same time interval between time points, whenever possible. See Visit Schedule – Section F.

1. The protocol will be revised in the section below: Participant Procedures, Section 3.C.6., page 27.

PRESENT TEXT:

Annual clinic visits will be scheduled to occur within a range of two months before to two months after the anniversary of the baseline enrollment date. [A2] Participants will experience many of the same procedures as those which occurred at the baseline visit.

REVISED TEXT: Add the following text:

Tests, questionnaires and physical measures originally scheduled during the Baseline Visit (Visit #3) and annual follow up visits can be completed within a broader time frame than described in the original protocol, without compromising the study integrity. The range has been re-defined such that any visit may be conducted until the time that the range (or visit window) for the next annual visit begins. This protocol deviation has been evaluated by the investigators and biostatisticians who have determined that this schedule adjustment can be accommodated, noting that the important factors are to collect data at uniform intervals during study participation and to strive to maintain this interval between time points, whenever possible. Therefore, variation in the conduct of telephone contacts, annual visits and the following tests will be permitted: I-GFR, EBT/MSCT, ECG and Echocardiogram.

B. Changes to Subcohort Selection – Evaluation and Procedure

The Scientific and Data Coordinating Center (SDCC) at the University of Pennsylvania has evaluated a different subcohort selection scheme to determine participant eligibility for two subcohort tests (I-GFR and cardiac CT/EBT). Originally the determination for subcohort selection and the paired tests was made based on I-GFR eligibility criteria. If a participant was eligible for GFR testing (and selected based on the statistical subcohort sampling schema), a participant was scheduled to receive I-GFR testing at the Baseline, Year 2 and Year 4 Visits, *and* cardiac CT/EBT testing at Year 1 and Year 4 visits, respectively.

The EBT Reading center at UCLA, under the direction of Matthew Budoff, MD, has recommended 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. An additional exclusion criteria for MSCT/EBT testing has been identified: Participants who weigh more than 300 pounds cannot be tested due to mechanical limitations.

The SDCC has proposed separating GFR from cardiac CT/EBT selection criteria and re-evaluating the cohort for participants who may be eligible for cardiac CT/EBT testing based on these criteria only. This will involve 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 changes to the test schedule and subcohort selection probability. The changes do not pose additional risk to CRIC Study participants.

1. The protocol will be revised in the sections below: Selection of Subjects for Nested Analyses, Section 3.A.3., page 19.

PRESENT TEXT:

We will adopt a purposeful, stratified weighted sampling strategy for selection of subjects for the iothalamate GFR and EBT cohorts based on anticipated distribution within the full cohort. During the initial enrollment phase, subjects will be chosen randomly for the iothalamate subcohort. After the enrollment of first 300 subjects, data will be analyzed to determine the distribution of the important predictor variables (e.g., eGFR) in the study cohort. If the distribution of eGFR appears appropriate (sufficient numbers of subjects with low and high values), we will continue selection of subcohort participants as before. If not, a sampling scheme will be adopted to ensure the adequate distribution of GFR among subcohort members. The scheme will involve random sampling with unequal probabilities of selection; the probabilities of selection will be based on eGFR or other variables, some values of which are poorly represented in the study cohort.

As with enrollment into the study, there will be targets for entry into the subcohort based on age, sex, and race. These ranges will be monitored carefully throughout the enrollment period and adjusted as necessary.

The subcohort selection process will be evaluated regularly over the course of study enrollment and varied while remaining random in a process called dynamic adaptive sampling, to ensure that the subcohort accurately reflects the overall cohort enrollment population based on the relative representation of a particular subgroup (i.e., gender, race, and diabetic status). [A2]

REVISED TEXT: Add the following text:

SUBCOHORT SELECTION, SAMPLING SCHEME, and TESTING SCHEDULE VARIATION

The Scientific and Data Coordinating Center (SDCC) at the University of Pennsylvania has evaluated a different subcohort selection scheme to determine participant eligibility for subcohort tests (I-GFR and cardiac CT/EBT). Previously the determination for subcohort selection and tests, was made based on I-GFR criteria. Prospectively,

eligibility for I-GFR testing and CT/EBT testing will be made independently. For example, a participant who is eligible for GFR testing (and selected based on the statistical subcohort sampling schema), will be scheduled to receive I-GFR testing. This same participant will be evaluated for CT/EBT eligibility and may or may not be selected for this test. Conversely, a participant who is ineligible for I-GFR testing may be eligible and selected for CT/EBT testing.

Participants who have had Coronary Artery Bypass Graft (CABG) surgery, coronary stenting or angioplasty will be excluded from cardiac CT/EBT testing, based on the visible changes introduced by these procedures. Participants whose weight exceeds 300 pounds will be excluded. Participants who were not originally selected for the subcohort will be evaluated and contacted to receive cardiac CT/EBT testing and to 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.

2. Exclusion Criteria, Section 3.C.5., page 24.

PRESENT TEXT: The following table lists exclusion criteria:

CRIC Study Exclusion Criteria

General Exclusion Criteria	
Institutionalized (e.g., prisoner, nursing home resident, skilled nursing facility resident)	Previously received dialysis (peritoneal and/or hemodialysis) lasting more than one month based on patient self-report
Unable or unwilling to provide informed consent	Prior organ or bone marrow transplant; prior renal transplant based on patient self-report
Participant appears unlikely or unable to participate in the required study procedures as assessed by the investigator, study coordinator or designee. [A1]	Received immunosuppressive or other immunotherapy for primary renal disease or systemic vasculitits that affects the kidneys (i.e., anti-GBM, ANCA, SLE, IgA nephropathy, cryoglobulin, etc.) within the past six months before enrollment based on patient self-report. This does not include, for example, use of prednisone for the treatment of reactive airways disease.
NYHA Class III or IV heart failure at baseline	Received chemotherapy or alkylating agents for systemic cancer other than non-melanoma skin cancer within two years prior to enrollment based on patient self report
Known cirrhosis based on patient self-report	Previous diagnosis of multiple myeloma or renal carcinoma based on patient self-report
Known HIV infection and/or AIDS based on patient self-report	Previously diagnosed polycystic kidney disease based on patient self report
Present participation in the AASK Cohort Study	Currently participating in an interventional clinical trial (i.e., primarily trials of therapeutic agents 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 that would preclude participation in CRIC are the AASK Cohort or KEEP Study. [A1]
Pregnant women [A2]	
Additional Exclusion Criteria for Participants Undergoing 125I-Iothalamate GFR Testing	
Known iodine allergy	Currently breast feeding, or pregnant based on urine HCG test
Impaired urinary voiding [A2]	Radiation exposure to γ-emitting isotope other than technetium

REVISED TEXT:

Table 9. CRIC Study Exclusion Criteria: The following exclusion criteria will be added for the CT/EBT procedure.

Additional Exclusion Criteria for Participants Undergoing CT/EBT Testing	
Participants who have had Coronary Artery Bypass Graft (CABG) surgery, coronary stenting or angioplasty [A3]	Participants whose weight is over 300lbs [A3]

C. CRIC Plus – Changes to the Core CRIC Protocol; Additional Data Collection for Participants Whose Estimated GFR (eGFR) Falls Below 20 ml/min/1.73m^2

The Chronic Renal Insufficiency Cohort (CRIC) study presents a unique opportunity to fill important gaps in knowledge regarding advanced chronic renal insufficiency, including the critical transition to end-stage renal disease (ESRD, defined as the initiation of dialysis or kidney transplant).

Virtually all published studies of incident ESRD patients begin at or after initiation of dialysis and do not have information regarding what transpired during the years prior to dialysis initiation. Conversely, the few prospective studies of chronic renal insufficiency patients have not continued follow-up into ESRD. In the original NIDDK RFA that led to the CRIC study, follow-up of patients after transition into end-stage renal disease was described. However, the original CRIC protocol is not optimized to study patients with advanced chronic renal insufficiency and their transition into ESRD.

Now with additional resources brought in as a result of the "CRIC-Plus" grant application, the CRIC core protocol will be augmented with more intensive data collection for subjects with advance chronic renal insufficiency (eGFR < 20 ml/min/1.73m^2). Newly enrolled participants will be consented with the revised consent form and participants currently enrolled will be asked to sign the revised consent form which includes the new study procedures applicable only to subjects who progress to estimated GFR < 20 ml/min/1.73m^2.

The core CRIC protocol is altered for CRIC participant's whose estimated GFR (eGFR) falls below 20 ml/min/1.73m^2 as follows:

Additional lab tests will include measured level of C-reactive protein (hs-CRP) using stored blood samples drawn from the study visit at which the estimated GFR falls below 20 ml/min/1.73m^2. All participants will have an echocardiogram when their estimated GFR falls below 20 ml/min/1.73m^2 (within 6 months) If this does not coincide with the core CRIC protocol echocardiogram at Years 1 and 4, an additional echocardiogram will be performed. For all subsequent yearly visits, participants with estimated GFR below 20 ml/min/1.73m^2 will be asked to undergo yearly (instead of every other year) bioelectrical impedance analysis (BIA) measurements. Participants with estimated GFR below 20 ml/min/1.73m^2 will be asked to attend a clinic visit instead of a telephone contact between annual visits to provide a 24-hour urine collection and undergo a blood draw for serum creatinine and blood urea nitrogen to calculate creatinine and urea clearance. The 6-month core CRIC protocol telephone contact information may also be completed during this visit. An echocardiogram will be scheduled should a patient developed ESRD (within 6 months).

These more intensive/frequent data collection will allow better capture of potentially rapid evolution of renal and cardiovascular disease status. CRIC participants whose GFR falls below 20 ml/min/1.73m^2 may have as many as four echocardiograms by the revised core protocol.

For CRIC participants who develop need for maintenance dialysis, the following additional dialysis-related information will be collected from the dialysis unit chart every 6 months:

1. Presumed cause of ESRD (collected only once)
2. Type of dialysis (hemodialysis vs. peritoneal dialysis with or without a cycler)
3. Information related to type of dialysis facility (e.g., for profit vs. not for profit)
4. Details of dialysis procedure itself (e.g., schedule and dose of dialysis, type of vascular access)
5. Treatment of renal failure complications (e.g., treatment of anemia, secondary hyperparathyroidism)
6. Measures of nutritional status (e.g., albumin, prealbumin, normalized protein catabolic rate)
7. Other routine blood chemistry measurements (e.g., serum potassium or calcium x phosphorus product)
8. Measures of residual renal function
9. Blood pressure (before and after hemodialysis session or at clinic visit for peritoneal dialysis patients)

For CRIC participants who receive a kidney transplantation, the following additional transplant data will be collected:

1. Source of transplant (e.g., cadaveric vs. living related vs. living unrelated)
2. Prior duration of dialysis before transplant

Participants will sign the appropriate medical record release forms.

Table 1 summarizes new protocol elements--applicable to participants whose e-GFR falls below 20 ml/min/1.73m^2.

Begins at CRIC visit when estimated GFR falls <20 ml/min/1.73m^2)		Study year after a participant's GFR fall < 20 ml/min/1.73m^2							
		0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0
CRIC CORE PROTOCOL									
Yearly CRIC core protocol data elements	X		x		x		x		x
6-month CRIC core protocol data elements		x		x		x		x	
NEW DATA COLLECTION FOR THOSE WHOSE GFR FALLS < 20 ml/min/1.73m^2									
24-hour urine collection (and blood draw)*	X	x	x	x	x	x	x	x	x
BIA¶	X		x		x		x		x
hs-CRP	X								
Echocardiogram†	X	A second echocardiogram will be performed if and when the patient develops ESRD							
Tracking of ESRD related variable		For patients who develop ESRD, ESRD related variables will be collected every six months							

* Increased from yearly 24-hour urine collections and blood draws scheduled in original core CRIC protocol.

¶ Bioelectrical impedance analysis only scheduled for baseline and years 2 and 4 in original core CRIC protocol.

† These are in addition to any echocardiograms scheduled in original core CRIC protocol years 1 and 4.

D. Ancillary Studies Associated with CRIC

The following four ancillary studies have been approved by the CRIC Steering Committee and are being incorporated into the CRIC Study at some but not all clinical centers. Each participating site will submit the ancillary study protocol and revised consent form to their IRB for approval before engaging in ancillary study activities. See the table in Section E which lists the ancillary studies and participating CRIC clinical centers. The Appendices include the complete protocol for the studies described below.

1. Retinopathy in Chronic Renal Insufficiency (RCRIC) Cohort Study

Since many of the CRIC Study participants are at high risk of developing significant retinopathy due to diabetes mellitus, systemic hypertension and other vascular diseases, it is important to assess the ocular condition. In addition, because both diabetic and hypertensive retinopathy have been shown to be associated with CRI and CVD, identification of these abnormalities in CRIC participants may improve predictive models aimed at identifying high risk subgroups with CRI.

The RCRIC research project will be an ancillary study to the CRIC study in which a single set of fundus photographs is obtained on CRIC participants either during their baseline visit or an annual visit marking 1, 2, or 3 years of participation in the CRIC Study. This spread over the years of participation in the CRIC study is due to the staggered recruitment of the CRIC study.

The RCRIC project will recruit 2200 volunteers from the 3000 subjects participating in the CRIC Study across the United States. Recruitment is planned to start in March 2006 and end in February 2007. Ages of the participants will be between 21 and 76 years at the time of enrollment. All participants will have some degree of

renal insufficiency, half of the participants will have Diabetes Mellitus, and about 75% will have systemic hypertension.

The RCRIC is a multicenter study that will be carried out in six Clinical Centers: 1) University of Pennsylvania Medical Center, Philadelphia, PA. 2) University of Maryland, Baltimore, MD. 3) University Hospitals of Cleveland, Cleveland, OH. 4) University of Michigan, Ann Arbor, MI. 5) University of Illinois, Chicago, IL. 6) Kaiser Permanente of California, Oakland, CA. It will be the responsibility of each clinical center to conduct the study according to the study protocol and applicable regulatory guidelines which will include the approval of this project by the IRB of each of the institutions involved. The Fundus Reading Center of the RCRIC study will be located in the Department of Ophthalmology at the University of Pennsylvania, Philadelphia, PA.

In all CRIC Study participants who agree to take part in our Retinopathy in CRI ancillary study, one set of fundus photography will be performed in both eyes with a non-mydriatic fundus camera that does not require pupillary dilatation.

A CRIC coordinator will present the purposes and detailed protocol of the ancillary study to all CRIC participants. Following signature of the consent form, the CRIC coordinator will obtain fundus photographs of the disk and macula of both eyes. Dilatation of the pupils is not necessary. Fundus photography will be obtained in a darkened room. To induce a natural dilatation of the pupil, a period of dark adaptation of about five minutes will precede photography. Time required to complete the photography will be about ten minutes.

A letter with information about the findings observed in the fundus photographs will be sent to the patients. Patients that have fundus findings that require treatment will be advised to seek a complete eye examination by their Ophthalmologist of choice. This ancillary study will pose minimal risks to participants.

2. Cognitive Function in Chronic Renal Insufficiency

Cognitive impairment is common in patients with end-stage renal disease (ESRD) although the etiology remains unclear. Both dialysis and renal transplantation appear to reverse these deficits. Correction of anemia with erythropoietin has been shown to improve cognitive function in anemic persons with ESRD. However, these interventions only partially correct the cognitive deficits associated with ESRD. Furthermore, the role of co-morbid conditions associated with both cognitive impairment and renal failure has not been well studied.

This study proposes to administer a battery of cognitive tests to participants enrolled in 3 of the 7 CRIC sites. These tests would be administered at the first possible annual CRIC clinic visit, or if necessary, at a separate study visit conducted close to the annual CRIC visit, and repeated at each annual visit thereafter. Given that age is the biggest risk factor for both cognitive impairment and for much comorbidity, cognitive testing will be obtained only on CRIC participants over age 55 years.

The choice of cognitive tests is driven by scientific goals, feasibility, ease of training and administration, prior use in CRI patients, and minimizing the burden to CRIC participants and CRIC staff. The current proposed battery of 5 tests would take approximately 40 minutes to administer.

- **Trails A and B (5 minutes):** measure visuospatial scanning, sequential processing, motor speed, executive function, and attention.
- **Category Fluency (2 minutes):** measures verbal production, semantic memory, and language with higher scores indicating better performance.
- **Modified Mini Mental Status Exam (3MS) (10-15 minutes):** a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory. Of note, this is not the same as the MMSE but provides complementary information and is more sensitive than the traditional MMSE. The 3MS is increasingly becoming a widely used cognitive test in epidemiological studies of aging. Using the 3MS in addition to the already collected MMSE is slightly redundant but provides expanded cognitive domains and would allow for inter-conversion with the shorter MMSE.

- **Buschke Selective Reminding Test (10-15 minutes):** The Buschke is a well-established validated test of verbal memory with immediate and delayed components.
- **Boston Naming (5 minutes):** a brief test of naming and language.

CRIC participants will be approached by the CRIC Study coordinator and will be asked to participate in the cognitive function ancillary study. Following signature of the appropriate consent form the tests will be administered by the CRIC coordinator at the time of the regular CRIC visit.

Participation in this study poses no additional risks.

3. Sleep Disturbances as a Non-Traditional Risk Factor for CKD

Sleep disturbances and poor quality sleep are common in patients with chronic kidney disease. Among patients with chronic renal failure, the prevelance of sleep apnea syndrome is estimated to be between 30-80%, which is much higher than the 2-4% prevalence in the general population. Additionally, approximately 80% of dialysis patients experience symptoms of restless legs syndrome. Thus, CKD patients may be at a greater risk of developing co-morbidities, such as cardiovascular disease and stroke that are known to be associated with impaired sleep. Furthermore, higher quality of life was significantly associated with lower daytime sleepiness in patients on hemodialysis.

There is also evidence to suggest that sleep disturbances will have an adverse effect on kidney function. Indeed, the hormones of the renin-angiotensin-aldosterone system exhibit large diurnal variations that are dependent on sleep.

Both plasma renin activity (PRA) and aldosterone levels are markedly elevated during sleep. The nocturnal increase in PRA and aldosterone levels is markedly blunted by acute total sleep deprivation and in conditions of abnormal sleep architecture. This blunting of the sleep-related increase in renin and aldosterone could play a role in the pathophysiology of chronic kidney disease.

The present study therefore seeks to explore the role of decreased sleep duration and/or quality as a risk factor for the progression of chronic renal insufficiency and the development of cardiovascular disease in CKD.

CRIC Study participants will be asked to sign the appropriate section of the informed consent document to indicate their willingness to participate in this ancillary study. The goal is to study a total sample size of 800. Collection of data will involve the distribution by mail of a well-validated wrist activity monitor (Actiwatch, Mini-Mitter Co. Inc. Bend, OR), and of validated questionnaires assessing sleep duration, sleep quality and depression (Karolinska Sleep Log, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, Berlin and Center for Epidemiologic Studies Depression questionnaires).

Patients will wear an Actiwatch on their wrist for 5 days continuously to record sleep. They will wear a second Actiwatch on one leg at night only to screen for periodic leg movements and obtain a measure of frequency and amplitude of leg movements.

Finally, they will complete the sleep log and questionnaires, and mail all instruments back to investigators. Two separate sleep assessments will be performed in each patient two years apart. Additionally we will request that insulin and C-reactive protein (CRP) be measured on a small aliquot (2 ml) of existing blood from the blood draw performed upon enrollment as well as on the blood drawn during the last year of the CRIC study period. This will not require an additional blood draw.

Participation in this study poses no additional risks.

4. Genetics of Atherosclerosis in Chronic Kidney Disease

Atherosclerotic cardiovascular disease (CVD) is the major cause of death in patients with end-stage renal disease (ESRD). The incidence and prevalence of ESRD in the United States continues to rise and is directly

related to a much larger and expanding population of patients with less severe chronic renal insufficiency (CRI). The risk of atherosclerotic CVD also appears to be increased in CRI compared to the general population. This may be due in part a higher prevalence of established atherosclerotic CVD risk factors in addition to unidentified factors that are likely to have a strong genetic basis. The genetic basis of atherosclerotic CVD has been established through family based heritability and linkage studies and candidate gene-association studies in multiple populatiuons.

The **metabolic syndrome (MetSyn),** a clustering of cardiovascular risk factors characterized by central obesity, insulin resistance, dyslipidemia and a pro-inflammatory state, is increasingly prevalent in our society. The prevalence of MS is increased in CRI. In fact, insulin resistance, raised triglycerides and low HDL are well recognized features of both CRI and ESRD and are believed to contribute to the progression of renal disease in addition to atherosclerotic CVD events. Low grade activation of innate immune **inflammation**, a feature of the MetSyn, is common a finding in CRI and ESRD. Epidemiologic and basic science studies suggest that activation of innate immunity is a proximal event in the MetSyn and is likely to contribute to its complications including diabetes, atherosclerotic CVD and possibly CRI. The mechanism of innate immunity activation in the MetSyn is unknown but appears to have a strong genetic basis and to be directly influenced by the amount of central adipose tissue, a rich source of inflammatory adipocytokines. Thus, the MetSyn and innate inflammation are major, non-traditional, candidate pathways for the promotion of atherosclerotic CVD in CRI and genes in these pathways may represent novel risk factors and therapeutic targets for CVD in CRI.

This study will will examine multiple CVD traits that provide mechanistic insight into our primary analyses of clinical CVD. Thus, we will determine the relationship of tagSNPs and estimated haplotypes in innate immune (Aim 1) and insulin resistance (Aim 2) genes (N=52) to (a) inflammatory and insulin resistance biomarkers, (b) coronary artery calcification (CAC), a direct measure of atherosclerosis, and (c) the risk of CVD. Further, we utilize re-sequencing data, generated by NIH-sponsored programs, to select tagSNPs in candidate genes for genotyping in the full cohort.

We propose to do additional EBT scans at 4 clinical centers (University of Pennsylvania, University of Michigan, Tulane University and Kaiser/Permanente). At these sites, we will invite all eligible subjects to undergo EBT scanning at their next or most convenient visit. Participants who are over the weight limit for the EBT scanner (>300lbs) or who have had procedures which interfere with the ability to read the EBT results (angioplasty with stent placement or coronary artery bypass surgery) will not be invited to have an EBT scan. The EBT scans will be read at the central reading center for the study and results will be provided to the participant and their physician.

For all CRIC subjects who have consented to genetic testing, DNA will be isolated from samples acquired during annual visits. High throughput genotyping will be performed for SNPs in genes related to inflammation and insulin resistance.

Additional time for EBT testing would be the main additional burden to both Clinical Center staff and their participants. The amount of time will depend upon the site and the waiting time at the EBT scanning facility. The total time of the scan is only about 15 minutes but this may have to be performed at a separate visit.

For all CRIC subjects who have consented to genetic testing, SNPs in genes related to inflammation. These samples are already collected and therefore this portion of the study does not involve any additional burden to participants.

E. Ancillary Study Table

Participating Clinical Sites	CRIC Plus Additional ESRD data added to Core protocol	Retinopathy CRIC Fundus Photography	Cognitive Function in CRI	Sleep Disturbances as CKD Risk Factor	Genetics of Atherosclerosis in CKD
Univ. of Penn	Yes	Yes	Yes	No	Yes
John Hopkins	Yes	No	No	No	No
Univ. of MD	Yes	Yes	No	No	No
Univ. Hosp. of Cleveland	Yes	Yes	No	Yes	No
Metrohealth	Yes	No	No	No	No
Cleveland Clinic	Yes	No	No	No	No
Univ. of MI	Yes	Yes	No	No	Yes
St. Johns	Yes	No	No	No	No
Wayne State	Yes	No	No	No	No
Univ. of Illinois at Chicago	Yes	Yes	Yes	Yes	No
Tulane	Yes	No	No	No	Yes
Kaiser/UCSF	Yes	Yes	Yes	No	Yes

F. Core CRIC Study Visit Schedule

CRIC Visit Schedule – Revised 12/22/2005	Pre-Screen	Screen-ing	Base-line	6 Mos.	12 Mos.	18 Mos.	24 Mos.	30 Mos.	36 Mos.	42 Mos.	48 Mos.	54 Mos.	60 Mos.
Type of Contact	Phone [V1]	Visit [V2]	Visit [V3]	Phone [V4]	Visit [V5]	Phone [V6]	Visit [V7]	Phone [V8]	Visit [V9]	Phone [V10]	Visit [V11]	Phone [V12]	Visit [V13]
Eligibility Assessment	X												
Informed Consent		X											
Medical Record Consent		X			X		X		X		X		X
Contact Information		X		X	X	X	X	X	X	X	X	X	X
Labs: Serum Creatinine, Serum Glucose		X											
Demographic Information		X											
Eligibility Confirmation		X	X										
Medical History [CV, Renal, Health Behaviors]			X		X		X		X		X		X
Genetic Blood Sample			X		X		X		X		X		X
Labs: CBC, Metabolic Panel, Lipids, etc.			X		X		X		X		X		X
Urinary Assay: 24 Hour Urine [Creatinine, Protein, Albumin, Urea Nitrogen]		X	X		X		X		X		X		X
Urine sample collection [A2]			X		X		X		X		X		X
Blood Pressure		X	X		X		X		X		X		X
Ankle Brachial Index & Anthropometric Measures			X		X		X		X		X		X
Bioelectrical Impedance Assessment [BIA]			X				X				X		
Nail Clippings			X		X		X		X		X		X
ECG			X		X		X		X		X		X
Echocardiogram					X						X		
EBT or MSCT (1/3 Subcohort Participants)					X						X		
I-GFR (1/3 Subcohort Participants)			X				X				X		
Pulse Wave Velocity Measure [alternating annual visits] [A2]			X				X				X		
Physical Activity Assessment			X				X				X		
Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X
MDRD Symptom Index			X		X		X		X		X		X
KDQOL - Quality of Life Questionnaire			X		X		X		X		X		X
Diet History Questionnaire			X				X				X		
Beck Depression Inventory			X				X				X		
Cognitive Function Testing [Mini Mental Status Exam]			X				X				X		
Cardiomyopathy Questionnaire – KCQ [A2]			X		X		X		X		X		X
Recent Medical History – Event Information				X	X	X	X	X	X	X	X	X	X