# CHRONIC RENAL INSUFFICIENCY COHORT (CRIC) STUDY


**Protocol Amendment #2**
**DATED: April 20, 2005**

Sponsored by the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Department of Health and Human Services (DHHS)


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## CRIC STUDY PROTOCOL - AMENDMENT 2

The changes listed below have been proposed to the CRIC Study Protocol, Version 2.0, dated, April 20, 2005, which includes Amendments #1 and #2. These changes have been approved by the CRIC Study Principal Investigators and the Steering Committee.

## PROPOSED AMENDMENT LISTING

**1. Subcohort selection process description**

a.) The text below will be added to Section 3.A.3., Selection of Subjects for Nested Analyses, page 19.

b.) 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 sub group (gender, race, diabetic status).

**2. Racial/ethnic group distribution**

a.) Approximately 10 months into the enrollment phase of the study it was evident that we would not be able to recruit the number of minority participants that were initially projected. Therefore, the proposed racial target distribution has been revised.

b.) The tables on pages 23 and 24 have been revised to reflect new recruitment target ranges.

| Racial Group | Final Proportion of CRIC | Adjusted Proportions (June 2004) |
|---|---|---|
| White | 40% | 47.5% |
| African-American/Black | 40% | 47.5% |
| Other | 20% | 5.0% |

**3. Additional exclusion criteria**

a.) Add the following text to the general exclusion criteria table on page 25:

Impaired urinary voiding will be evaluated by the investigator in terms of problems emptying bladder, awakening to urinate, incontinence, history of prostate problems and recent urinary tract infection.

b.) Add the following text to the general exclusion criteria table on page 25:

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 made or questionnaires administered during clinical follow-up visits. If a woman is found to be pregnant after screening but before the baseline visit has occurred, she will be withdrawn and can be re-screened approximately one year later.

**4. Interval between screening and baseline visits**

a.) The text below will replace the sentence in the second paragraph on page 26, which defines the interval between the screening and baseline visits. Initially, this interval was 30 to 45 days; however, it has become necessary for participant scheduling convenience to increase this interval to 3 months.

**OLD TEXT**

If a person is eligible according to the information collected during the screening visit, she/he will be scheduled within 30 to 45 days for a baseline visit.

**NEW TEXT**

If a person is eligible according to the information collected during the screening visit, he/she will be scheduled to return within **3 months** for a baseline visit.

**5. Clarification to the 24 hour urine collection test**

a.) The text below will replace the statement on page 26 to provide clarification about the conduct of the 24 hour urine test.

**OLD TEXT**

Instructions and supplies will be provided for the collection of a 24 hour urine sample for use in the event the eGFR calculation identifies the potential participant as eligible. If eligible, participants will be instructed to complete a food frequency questionnaire that asks detailed information about the food they eat and return the completed questionnaire at the baseline visit. Participants selected for the subcohort studies will be informed of this shortly after this visit to prepare for the baseline visit procedures.

**NEW TEXT**

During the screening visit, participants who have completed the screening process are provided supplies and instructed about how to collect a 24 hour urine sample. When a participant's study eligibility is confirmed, which is shortly after the screening visit (Visit 2), they are contacted by study personnel who will review the urine test directions and instruct the participant to collect the 24 hour sample just prior to the next study visit, which is the baseline visit (Visit 3), and bring it with them to this visit.

**6. Additional urine sample at each annual clinic visit.**

The text below will be added to Section 3.C.6. Participant Procedures, page 26, and to the visit schedule to reflect the collection of this sample at the baseline visit and subsequent annual visits.

A "clean catch" urine sample will be collected at the baseline visit and annually from all participants. Approximately 100 cc will be reserved for storage.

**7. Annual Visit Schedule**

a.) Section 3.C.6., Participant Procedures, page 26, will be revised to reflect the changes to contact time surrounding annual visits.

**OLD TEXT**

***Annual clinic visits*** will be scheduled to occur within a range of one month before to one month after the anniversary of the baseline enrollment date.

**NEW TEXT**

***Annual clinic visits*** will be scheduled to occur within a range of two months before to two months [A2] after the anniversary of the baseline enrollment date.

**8. Additional physical activity measure**

a.) The text below will be added to Section 3.D.1., Study Data, Physical Activity, page 28.

b.) The modified Kansas City Questionnaire will be used to evaluate physical activity and the presence or worsening of cardiomyopathy symptoms. This questionnaire will be administered to all participants annually.

**9. Permit Multi-Slice Spiral Computerized Tomography (MSCT) scanning technology in addition to Electron Beam Tomography (EBT) as a modality to measure coronary calcium in subcohort participants**

a.) The text below will be added to Section 3.D.3.B., Cardiovascular Tests, Coronary Calcium Assessment by Electron Beam Tomography (EBT), page 34, to describe the feasibility of using MSCT as well as EBT to measure coronary calcium.

b.) 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.

**10. Pulse Wave Velocity and Vascular Compliance Procedure added to procedures performed on all participants to occur on alternating study visits (every two years)**

a.) The text below will be added to Section 3.C.6. Participant Procedures, page 26, and to the visit schedule as well as Section 3.D.3.B., Cardiovascular Testing, following the description of Ankle-Brachial Index, page 36.

Measures of Aortic Pulse Wave Velocity (APWV) in CKD patients could improve upon the predictive power of blood pressure measurement for CKD and CVD endpoints. In a related subset of CKD patients on hemodialysis, measurement of aortic APWV provides independently predictive information on the potential for target damage, including heart failure, stroke and CV death when compared to systolic, diastolic or pulse pressure measurements.{Blacher, 1999 2482 /id;London, 2001 2480 /id}

Evaluating a large body of cardiovascular outcome evidence over the last decade suggests that diastolic blood pressure is a strong predictor in younger (< 50 year old) patients. Between the ages of 50-59 no single blood pressure measure (systolic, diastolic or pulse pressure) has clear dominance, and beyond 59 years of age the systolic blood pressure and more recently the pulse pressure becomes particularly predictive of CV events.{Franklin, 2000 2481 /id} The diastolic pressure is related more to the systemic vascular resistance than stiffness, the systolic pressure more to arterial stiffness, and the pulse pressure appears to be the blood pressure measure most related to arterial stiffness. Thus, with brachial arterial blood pressure measures, the more closely they center on arterial stiffness, the more predictive of CV endpoints they become.

While the predictive value of brachial blood pressure in predicting CV events is well established, it shortcomings are perhaps best summarized in the following quote from the Medical Research Council Trial of Hypertension in 1985 (which, at the time, was the single largest randomized controlled trial in hypertension, analyzing data on >85,000 patient years of follow-up) “The trial has shown that if 850 mildly hypertensive patients are given active antihypertensive drugs for one year about one stroke will be prevented. This is an important but an infrequent benefit. … More than 95% of the control patients remained free of any cardiovascular event during

the trial."{Greenberg, 1985 2483 /id} We treat most hypertensives to prevent target organ damage in a subset. Thus, knowledge of the blood pressure, even in conjunction with other CV risk factors as in this MRC trial, has room for improvement in that other vascular measures (such as those proposed in this ancillary study) potentially could add to the assessment of CV event likelihood and provide a means by which we can better assess CKD progression and CV risk in patients.

Participants will be asked to have two noninvasive tests that evaluate how blood vessels adapt to each heartbeat. Three ECG leads are placed on the torso while the participant is lying on their back. Distance is measured from the suprasternal notch to the carotid and femoral arteries and a probe measures the pulse at these points and the radial artery. The probe is adjusted until an acceptable waveform has been generated and measurements have been acquired which will take approximately 15 minutes. The device used is FDA approved for research but results are not typically used to manage health care. There are no known risks associated with the test.

**11. Procedures for following subjects who reach ESRD**

a.) The text below will be added to Section 3.E.5., Special Considerations for the Study of Progression of Renal Disease, page 45.

b.) Participants who begin dialysis or receive a kidney transplant will be asked to provide additional information in the form of a brief questionnaire that asks focused questions about the procedure and their preparation and experience. To whatever extent possible, these participants will be followed according to the study protocol.

**12. Initial review of ECG's performed during the annual visit**

a.) The text below will be added to Section 4.B.1., Transmission of Study Findings and Response Time, page 54, and Appendix D, Table of Clinical Alert Values and CRIC Response Time, page 88.

b.) The time frame for local review for the presence of urgent ECG alerts has been increased from 24 to 72 hours. This was necessary as it was not always possible for all sites to arrange this review by a center physician.

**13. Report CRIC study measures to participants and HCPs**

a.) Section 4.B.1., Transmission of Study Findings and Response Time, page 54, will be revised to reflect the changes to reporting time of CRIC research measures and laboratory results.

**OLD TEXT**

An initial report will be mailed approximately one month after the baseline visit and will include results of routine laboratory results indicated above, as available. A

second report will be mailed 4-6 months after the completion of the additional tests, which may include ECHO, EBT, GFR and any outstanding laboratory results.

**NEW TEXT**

The schedule for reporting CRIC information to participants and their health care provider has been revised to reflect the accumulation of lab test results from several laboratories that requires approximately 6 – 8 weeks for the initial (primary) report and 4 – 5 months for tests acquired at a later date or batch tested.

**14. Revised Visit Schedule – Appendix A, page 86**

The visit schedule includes the following added questionnaire and procedures:

- Pulse Wave Velocity measure conducted on alternate years
- Additional "clean catch" urine sample collected annually
- Cardiomyopathy questionnaire administered annually

## References


17. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation. 1999; 99:2434-39.

38. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. Hypertension. 2001; 38:434-38.

39. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation. 2001;103:1245-49.

40. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. Br Med J (Clin Res Ed). 1985; 291:97-104