CHRONIC RENAL INSUFFICIENCY COHORT (CRIC) STUDY

Protocol Amendment #4
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Visit Schedule Revised: March 13, 2006

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PROTOCOL AMENDMENT #4

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 protocol changes listed below refer to the CRIC Study Protocol, Version 2.0, dated, April 20, 2005, which includes:

Amendment #1, dated March 17, 2003,

Amendment #2, dated April 20, 2005, and

Amendment #3 dated December 22, 2005.

A revised informed consent form is included which reflects the changes described in this amendment. Please see the Table of Contents. The changes proposed in this document have been approved by the CRIC Study Principal Investigators and the Steering Committee.

CRIC STUDY PROPOSED AMENDMENT LISTING

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A Enrollment

A.1 Recruitment Goals

This memo seeks to address a change to the CRIC Study protocol regarding the enrollment goals of each of the participating clinical centers. The enrollment goals established by the seven participating clinical centers at the start of the CRIC Study in 2003 have been revised to account for the loss of participants from Tulane University, New Orleans, as a result of the Hurricane Katrina disaster. Though the CRIC Study site at Tulane is the process of reorganizing its center and staff, it is unknown at this time how CRIC Study follow-up among Tulane participants will progress. Therefore, the remaining clinical centers have agreed to enroll additional 50 - 80 participants to account for the potential loss of participants at the Tulane clinical center.

A.1.a Clinical Centers

The seven clinical research centers of the CRIC Study include:

1. University of Pennsylvania
2. Johns Hopkins University/University of Maryland
3. Case Western Reserve University/University Hospitals of Cleveland
4. University of Michigan at Ann Arbor
5. University of Illinois at Chicago
6. Tulane University Health Science Center
7. Kaiser Permanente of Northern California/University of California at San Francisco.

The Scientific and Data Coordinating Center for the CRIC Study is located at the University of Pennsylvania.

A.1.b Recruitment Phase

The recruitment phase will be extended through December 31, 2006. (The original recruitment phase of the study was 33 months long, from July 2003 until March 2006.) It is projected that this extension will result in accomplishment of the study enrollment targets. To date, clinical centers have been successful in achieving the recruitment goals established at the start of the study.

These changes were approved by the CRIC Study Scientific Advisory Committee and the Steering Committee on January 30, 2006. The CRIC Study Protocol, Version 2, will be revised to reflect these changes in the sections below:

A.2 Protocol Text Changes

A.2.a Study Patient Population and Sample Distribution (Section 3.C., Page 21)

Present Text:
Each of the seven Clinical Centers will plan to enroll approximately 430-500 participants. The final center-specific recruitment approach will take into consideration the observed rate of loss-to-follow-up during the first study year and be chosen to establish the cohort of 3000 CRIC participants who undergo a baseline and the Year 1 follow-up visit. [A2] The estimated rate of

dropout during the first year is estimated at 3 – 5 %. This phase will occur over a 33-month period beginning in Year 2 of the overall study calendar.

Revised Text:
Six of seven CRIC clinical research centers will continue to recruit and enroll participants. The CRIC site at Tulane, which was not operational between September and December 2005, has now resumed follow-up activities after spending the last several months attempting to contact study participants.

Each of the six Clinical Centers will plan to enroll an additional 50-80 participants, which will result in approximately 520-550 participants per center. The final center-specific recruitment approach will take into consideration the observed rate of loss-to-follow-up during the first study year and be chosen to establish a cohort of CRIC participants, 3000 of whom successfully participate in the Year 1 follow-up visit. This phase will occur over a 42-month period beginning in Year 2 of the overall study calendar.

A.2.b Recruitment (Section 4.A.1., Page 53)

Present Text:
Sources of participants will vary from center to center. Likely sources include computerized searches of databases, hand searches of medical records of health care providers, referrals from health care providers other than CRIC investigators, and the patient panels of CRIC investigators. The recruitment goal is challenging, namely, 3,000 participants who complete not only the baseline visit but also the first annual follow-up visit. Each of the seven Clinical Centers will plan to enroll approximately 430-500 participants.

Revised Text:
Sources of participants will vary from center to center. Likely sources include computerized searches of databases, hand searches of medical records of health care providers, referrals from health care providers other than CRIC investigators, and the patient panels of CRIC investigators. The recruitment goal is challenging, namely, 3,000 participants who successfully complete not only the baseline visit but also the first annual follow-up visit. To account for loss of recruitment and anticipated incomplete follow-up at the Tulane site, each of the six Clinical Centers will plan to enroll an additional 50-80 participants, approximately 520–550 participants.

B Bioelectrical Impedance Analysis (BIA) Procedure Schedule Change (See Visit Schedule)

BIA is described in the protocol in the section entitled **Assessment of Dietary Intake**. (See page 28.)

Additional Information:
Currently BIA is measured at baseline and alternating annual clinic visits following the baseline visit. This amendment proposes to measure BIA at the baseline visit and annually at the clinic visits following the baseline visit. This change will be reflected in the revised visit schedule and revised consent form.

C Changes to Amendment 3: Additional Data Collection in Participants Who Develop Advanced Chronic Renal Insufficiency

Amendment 3 indicated that participants whose estimated GFR (eGFR) falls below 20 ml/min/1.73m^2 would participate in CRIC Plus. CRIC Plus, as explained in Amendment 3, extends the CRIC core protocol to allow for more intensive data collection for subjects with advanced chronic renal insufficiency (eGFR < 20 ml/min/1.73m^2). CRIC Plus participants were to 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 renal clearance.

On further review of this issue, considering participants' time and effort, the Steering Committee decided to modify this set of activities and eliminate the additional clinic visit, reverting back to the telephone contacts between the annual clinic visits. As a result, the additional blood draw and 24-hour urine sample, described in Amendment 3, will be eliminated. Participants who reach this stage of renal disease will experience the same CRIC visit schedule as originally described. As such, the six month visit will be a phone contact as previously described.

Furthermore, to ensure a smooth transition, the CRIC Plus activities will be triggered and apply not only to CRIC subjects whose eGFR is observed to fall <20 ml/min/1.73m^2 but also to CRIC subjects with high likelihood of progressing to an eGFR <20 ml/min/1.73m^2 based on the observed and projected trajectory of renal function. Projected likelihood will be estimated using a multivariable regression formula developed for this purpose within CRIC. Relevant CRIC Plus activities include obtaining an additional echocardiogram and measurement of hs-CRP.

As described in Amendment 3, because of CRIC Plus, a CRIC participant may have as many as four echocardiograms; at the year 1 annual visit, year 4 annual visit, once estimated GFR (eGFR) falls below 20 ml/min/1.73m^2 , and at the onset of Renal Replacement Therapy (RRT). For CRIC participants who develop the need for maintenance dialysis or renal transplantation, additional dialysis or transplant-related data would have been collected from the dialysis unit or transplant center medical records every 6 months. This Amendment 4 modifies, to annually, the frequency with which dialysis or transplant-related information will be collected.

Newly enrolled participants will be consented using the new consent form that describes these procedures. Participants who are currently enrolled will be asked to sign a revised consent form that reflects the protocol changes associated with CRIC Plus.

D Core CRIC Study Visit Schedule

CRIC Visit Schedule – Revised 03/13/2006	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] **[A4*]**			X		X*		X		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

† hs-CRP will be measured when a patient develops observed or projected eGFR < 20 ml/min/1.73m^2 **[A3 and A4]**

*Additional echocardiograms will be performed if and when a patient develops observed or projected eGFR < 20 ml/min/1.73m^2 and if and when the patient develops ESRD **[A3 and A4]**

For patients who develop ESRD, ESRD related variables will be collected every year **[A3 and A4]

E Core CRIC Informed Consent Form