Chronic Renal Insufficiency Cohort (CRIC) Study

Ancillary Studies Policy

I. General Policy

To enhance the value of the CRIC Study, the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies. To protect the integrity of the CRIC Study, the Primary and Ancillary Studies Committee and the Steering Committee must review and approve all proposed ancillary studies before their inception or submission of a proposal for external funding consideration.

II. Definition of an Ancillary Study

An ancillary study is one based on information derived from CRIC Study participants in an investigation or analysis that is relevant to, yet not described in, the CRIC Study protocol, and that derives support from non-CRIC Study funds. A typical ancillary study will propose the collection of additional data not collected or analyzed as part of the routine CRIC Study data set. Ancillary studies may be submitted by the investigators within the CRIC Study or by investigators without a prior relationship to the CRIC Study. Ancillary studies require external (non-CRIC Study) funding to cover all associated costs. Examples include studies funded by investigator-initiated NIH research awards (RO1s), grants from academic institutions or private sources (e.g., private foundations, pharmaceutical companies). Any ancillary study must have sufficient funding to cover the costs incurred by the CRIC Study clinical centers and laboratories (e.g., to process or to ship samples) and by the scientific and data coordinating center (for tasks such as sample selection, preparing and documenting analysis files, participating in statistical analysis, and integrating the new ancillary data back into the combined CRIC Study database).

III. Requirements and Procedures for Approval of an Ancillary Study

III. A. Overview

Participation in, and approval of an ancillary study is subject to review by the CRIC Primary and Ancillary Studies Committee and to formal approval by the CRIC Steering Committee. Under specific, selected conditions (e.g., an imminent funding deadline), the CRIC Executive Committee may serve as the proxy for the Steering Committee, although this is expected to be a relatively uncommon situation. Approval by the Steering Committee requires seven of nine votes in favor of the proposal. Dissenting voters must provide the explicit reason for their dissent. Any issues of concern to dissenting voters are shared with the applicant and opportunities for clarification provided. All sites (clinical centers, scientific and data coordinating center, NIH) agree to cooperate with approved ancillary studies regardless of their individual vote.

Ancillary study investigators must receive approval of their concept, and then engage in detailed budget and scientific planning in cooperation with the SDCC and participating clinical center investigators before submitting their grant to any funding agency. Potential ancillary investigators are strongly encouraged to discuss potential proposals with the chair or co-chair of the Primary and Ancillary Studies Committee, or the study chair of the CRIC Study before submitting a concept proposal.

All within-CRIC ancillary study proposals must include at least one CRIC investigator as a co-investigator. Willingness to include additional CRIC investigators as co-investigators of the ancillary study is mandatory, and potential ancillary investigators must document that they have contacted the principal investigators (PIs) of all clinical centers to determine their interest in participating in the ancillary study. If another site wishes to participate in the ancillary study, the PIs may contact the proposing investigator directly with the assistance of the chair or co-chair of the Primary and Ancillary Studies Committee, if needed.

III. B. Proposals for Ancillary Studies as Part of Training or Career Awards

The CRIC Study investigators and the NIH anticipate that the CRIC Study will be an important resource for career development and training among members of the academic community. Therefore, proposals for ancillary studies to be funded through training grants or career development awards through the NIH or other funding sources require special consideration. As these funding mechanisms typically provide funding only for investigator effort, not for additional data collection, such proposals will generally propose research questions and analyses that could be considered part of the core CRIC Study. In these cases, consideration of what analyses will be authorized could present a conflict with the interests of the CRIC investigators. Evaluation should consider the scientific gain to the CRIC study from the addition of the proposed ancillary analyses as well as the training and career development opportunities afforded to the applicant by the proposed ancillary study.

Evaluation in the case of proposals to be funded through training grants is limited to trainees of CRIC study investigators, as the quality of the analyses will be greatly dependent on the mentor identified in the training grant. In the case of faculty career awards, evaluation of ancillary study applications will need to consider the anticipated scientific contribution of the applicant, including the applicant's ability to perform data analyses that the SDCC may not be able to perform without additional funding. Further, willingness to adhere to the requirements of the Publications and Presentations Committee with respect to authorship will be particularly important.

The review process will have several steps. The first step is registration of the proposal concept. This may occur up to one year before an anticipated submission date. Proposal concepts should be registered on the CRIC website. Once a concept proposal document is generated, the next step is review of the proposal concept and acceptability by the Primary and Ancillary Studies Committee. The proposal concept should be summarized in 2- 4 pages.

III. C. Considerations for Approval

1. The proposed study must meet requirements of the highest scientific merit.

2. Participant burden:
    a. The proposed study must be acceptable to the participants (e.g., time, discomfort, privacy).
    b. The proposed study must not interfere with other parts of the main CRIC Study.
    c. The proposed study must not hamper continued participation in the main CRIC Study.
    d. The proposed study must put minimal demand on scarce CRIC Study resources such as blood samples.

3. The proposed study must require the unique characteristics of the CRIC Study cohort to accomplish its goals.

4. The investigators must have adequate resources to effectively complete the project, including:
    a. Sufficient budget and personnel
    b. Staff having the requisite expertise to meet the objectives of the project.

5. The ancillary study investigators must agree to return the complete ancillary data set back to the CRIC Study if requested by the CRIC Study Steering Committee.

6. The proposed study must not interfere with the completion of the main objectives of the CRIC Study.

7. The proposed study must not adversely affect participant cooperation or compliance with the CRIC Study.

8. The proposed study must not create a serious diversion of study resources (personnel, equipment, or study samples) or investigator/staff time, either locally or centrally.

9. The proposed study must not jeopardize the public image of the CRIC Study.

10. The proposed study must have documented involvement of the CRIC investigators as part of the research team.

III. D. Instructions for Preparation of Requests for Approval of an Ancillary Study

Before submission to a funding agency, all proposed ancillary studies must be submitted to the CRIC Primary and Ancillary Studies Committee in time for circulation and subsequent review by the Steering Committee. Studies submitted for review less than 8 weeks before a funding application deadline may not receive approval. Under specific conditions (e.g., an imminent funding deadline) the CRIC Executive Committee may serve as the proxy for the Steering Committee.

III. E. Proposal Format

The following elements must be included in an ancillary study proposal:

1. ***Participation of other CRIC centers.*** Before submitting the proposal for the first review within PAM, each investigator must consider the possible participation of other CRIC centers.

2. ***Registration of the concept.*** The website (www.cristudy.org) will soon have a link to register the concept an investigator wishes to pursue with an ancillary study. Registration of this concept generates an electronic message sent to all CRIC sites and broadcasts the investigator's interest in developing the protocol. There will be times when the study cannot accommodate all interested sites because of budgetary constraints. It is important that adequate communication exists before sites are included/excluded. The Steering Committee will ultimately arbitrate any process in which a dispute arises regarding an ancillary study and site exclusion based on budget (or any other) constraints.

A written request for approval of an ancillary study should be submitted to the Primary and Ancillary Studies Committee as a 2- to 3-page summary containing the following information:

1. Identifiers
   a. Initiating investigators, collaborators, CRIC Study co-investigator
   b. Confirmation of participation status of all CRIC clinical centers and the SDCC
   c. Planned starting date and project timeline
   d. Funding plans and estimated cost

2. Design and Methods
   a. Brief background and rationale
   b. Study questions or hypotheses
   c. Specific data collection methodology, including questionnaires and coding forms, if available.

3. Specific Answers to the Following Questions
   a. What is the expected burden to participants? What are the specific time burdens, discomfort, and expected participation rates?
   b. What CRIC Study core data and/or analyses are needed for the ancillary study?
   c. Is blood or other biologic samples (either fresh or from the CRIC Study's repository of stored samples) required? What will be the quantity of specimens needed?
   d. What collaboration with CRIC Study investigators is planned? With whom? Have the collaborating investigators approved the proposal?
   e. What, if any, follow-up is needed? Specify length of time and events to be ascertained.
   f. How many participants are required?
   g. When will data be collected? Could the ancillary study be deferred to a later exam cycle?
   h. How will the ancillary study be funded? Would any additional un-reimbursed work or personnel time be expected of the CRIC Study? How will the ancillary study budget cover demands on CRIC Study personnel time and resources?
   i. Where will the data analyses be conducted?

j. How will the confidentiality and other aspects of protection of human subjects be maintained?
k. When and in what form will a complete data set be returned to the CRIC Study?

4. Data or Specimen Requirements

a. Data needed from CRIC Study analysis files
b. Specimens needed from CRIC Study repositories, specifying type and amount

5. Handling of CRIC Study Data and Specimens

a. Disposition of stored samples from main study and those processed by ancillary study
b. Disposition of ancillary study data at the conclusion of the ancillary study

Beginning with the October 2003 NIH deadlines, all ancillary study proposals should be initiated at least 4 months before the due date of the agency to which it is anticipated that the proposal will be submitted. All potential investigators are strongly encouraged to contact Eunice Franklin-Becker at the SDCC (efrankli@cceb.med.upenn.edu or 215-573-9359) as early as possible in the process. The SDCC participates in budget development and is integral to planning study design and analyses. Study logistics, including data collection, data management, and storage, and analytic plans have profound budgetary impact and must be developed in cooperation with the SDCC.

IV. Changes to Proposed Study

Once an ancillary study is approved, if a change occurs in the structure or concept of the study, such changes should be disclosed to the Primary and Ancillary Studies Committee and to the CRIC Steering Committee for review and approval.

V. Proposal Budget

The investigator applying for an ancillary study must supply all additional funds needed to successfully complete the study. The Primary and Ancillary Studies Committee will be concerned with both the obvious and the hidden costs to the CRIC Study that are entailed by an ancillary study. Provision of funds for these expenses is essential—an ancillary study cannot begin without such fiscal support to the core study. The need for such support must be stressed in research grant applications because this support is a mandatory ingredient. Such costs include, but are not limited to, the following:

1. Statistical and data management staff for coordinating the additional data management and analyses

2. CRIC Study expenses involved in altering key identifying data so that subjects' confidentiality will be protected

3. Costs for notification of alert values

4. If work is to occur on site, rental of appropriate clinic, lab, and office space

5. If subject recruitment outside of main exams is anticipated, a subject coordinator to arrange subject appointment

6. Personnel, equipment, and supplies necessary to complete the project

Once a study concept is approved, applicants for ancillary studies must work in conjunction with the SDCC to develop a budget that adequately provides for these types of expenses at both the SDCC and Clinical Centers. This requires submission of a more detailed study proposal to the SDCC for use in budget development soon after the proposed study is approved.

VI. Human Subjects/Data Confidentiality

Confidentiality of CRIC participants must be guaranteed. Individually identifiable data may not be released. A signed consent must be obtained from every participant in the ancillary study, if the data collection/request is not covered in the original informed consent process for the main CRIC Study.

1. Any investigator or personnel having access to CRIC subject data should have received an orientation on the CRIC Study confidentiality policy. Key personnel of the ancillary study must be certified in the NIH OHSR or equivalent training course.

2. A copy of the IRB letter for the ancillary study is to be sent to the Scientific Project Manager at the Scientific and Data Coordinating Center. If a separate consent form is required for the ancillary study, a copy of the signed ancillary study consent form for each study participant must be included in the CRIC Study record.

3. A data file tracking all signed ancillary consent forms must be maintained by the ancillary study and an electronic copy of that file must be delivered to the CRIC Study.

The principal investigator of an ancillary study is responsible for presenting the study to the Primary and Ancillary Studies Committee or Steering Committee as appropriate, monitoring the study to assure continuing compatibility with CRIC Study and serving as a liaison to the CRIC Steering Committee. The CRIC Steering Committee monitors the development of the ancillary studies, receipt of funding, initiation dates, and progress. A written progress report on ancillary studies must be made periodically to the Steering Committee and the Monitoring Board.

VII. Analysis and Publication of Results of Ancillary Studies

Unless specifically arranged, all analyses will take place at the SDCC and be conducted under the supervision of its biostatistician-investigators. Under specifically approved circumstances

datasets will be released for analysis by external investigators. Ancillary studies funded as career or training awards as well as studies taking place in a subset of clinical centers may be situations in which release of data for analysis deserves special consideration. Under these circumstances, the investigator of the ancillary study will provide interim reports on analyses to the SDCC during data analysis to ensure that all study data used in analysis of ancillary study results are consistent with data in the main study database and to ensure the quality of analytical approaches.

Proposals for manuscripts resulting from all ancillary studies shall be submitted for review to the Presentations and Publications Committee and require approval by the Steering Committee before establishment of a writing committee or a submission for publication or presentation. It is anticipated that principal investigators of approved ancillary studies will lead at least one scientific paper emerging from the ancillary study analyses as specified in the Publications and Presentations Policy. Each manuscript and abstract would be expected to include a CRIC investigator. The phrase "CRIC Study" should be included in the title in all scientific presentations and manuscripts and listed as a key word whenever possible. Manuscripts will also contain an appendix listing CRIC investigators who are deemed appropriate.

VII. Feedback of Results of Ancillary Studies to Participants

Results of ancillary studies shall be reported to participants and/or their physicians if medically useful. Such reporting should follow standard CRIC protocol for notification of participants.

VIII. Handling of CRIC Data and Specimens

At the time of distribution of CRIC specimens and/or information, the CRIC collaborating investigator, with help from the coordinating center, will make explicit arrangements with the ancillary study PI for the security of these study materials and for their final disposition at the conclusion of the ancillary study. The safety and confidentiality of the CRIC data at the collaborating institution is the responsibility of the ancillary study PI, as is the appropriate disposition of these materials after the study has been completed. Leftover DNA and laboratory specimens are destroyed or returned, and files of CRIC data are returned or deleted, as established at the outset of the collaboration.

An archival copy of the newly collected data and/or laboratory results not already held at the SDCC will be sent to the CRIC coordinating center at the conclusion of the data analysis and publication of the main (ancillary) study hypothesis. This transfer is the responsibility of the ancillary study CRIC collaborator(s). Once transferred back to the CRIC, these ancillary data will become part of the aggregate CRIC data. Subsequent access to these data will be governed by the CRIC Study Policy on Use of Archived Study Data.

IX. Site Responses to Ancillary Study Submissions

The Steering Committee ballot for each ancillary study will contain a section in which the interest of each site in participating in the ancillary study is formally registered. In addition to voting either 'No', 'Yes', or a 'qualified Yes' (with attached comments), each site will indicate one of three levels of desired involvement as follow below in a hypothetical ancillary study ballot:

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CRIC Ancillary Study Sample Ballot – Distributed February 28, 2003

Ancillary Study Title: **Life with Renal Failure**

Please check one of the following responses and include detailed explanations where appropriate. Please forward electronically your completed ballot to Eunice Franklin- Becker (efrankli@cceb.med.upenn.edu) by ***March 14, 2003***. No response will be considered approval. Please 'cc' your email comments to: townsend@mail.med.upenn.edu

_____ Yes, I approve the above Ancillary Study

_____ Yes, I approve the above Ancillary Study with the following modifications:

_____ No, I do not approve the above Ancillary Study (please explain below):

Our proposed site participation:

_____ No interest

_____ Partial interest (scientifically engaged, wish to contribute intellectual content, but do not wish to perform additional data collection at our site; no budgetary needs)

_____ Full Interest (scientifically engaged, wish to contribute intellectual content and to collect data at our site; include in budgetary considerations as appropriate below)

____ a) data collection and investigator salary support

_____ b) investigator salary support alone

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Section 2: Training Grant Ancillary Submissions:

We recognize the need to both protect the integrity of the core hypotheses and yet provide for research training in junior members of our various institutions. The ancillary submission form is now amended to include a box to check for "Training Proposal" which will alter the philosophy of the review process within the PAM sub-committee as well as the Steering Committee.

When a Training proposal is submitted, we now ask for a paragraph from the mentor(s) indicating briefly their credibility as mentors in the proposed training area, and their commitment to the individual. Attaching a CV of the mentors is welcomed, but not necessary. Hopefully we can establish a CV link in the CRIStudy.org website so that when the proposal circulates the mentor's CV(s) could be easily accessed if a reviewing individual is interested.

Since "hypothesis overlap" is likely, if not probable, a paragraph in the proposal dealing with whether, and exactly how, the overlap is to be handled is necessary. Since this is a process, the 'requirements' for this paragraph are vague, and guidelines for this are necessarily general. The paragraph should acknowledge where overlap exists. When substantial overlap exists, how this proposal will add to CRIC as well as to the development of the research aim(s) should be explained. It is strongly recommended to contact and discuss these proposals within the PAM sub-committee as well as with the SDCC. We encourage ancillary proposals, and we all want to foster training in nephrology. However, there will be circumstances in which the overlap with primary hypotheses is too large to be considered approvable by the Steering Committee. It is best to discuss the proposals candidly with members of the Steering Committee when this is anticipated.

When the proposal circulates through the PAM sub-committee, the Training Proposal box tick will generate the following checklist in addition to the usual considerations for any ancillary proposal:

__ Does the hypothesis overlap with core hypotheses in CRIC, and has rationale supporting why the overlap is reasonable been presented?

__ Is the mentor(s) clearly identified and do they appear to possess the expertise and commitment to train the candidate?

__ Will the proposal require resources clearly beyond those typically available in a training award, and does the mentor have such resources available?

Section 3: Ancillary Submissions from Investigators Outside of the 7 Clinical CRIC Centers:

The External Scientific Advisory Committee has recommended to the CRIC Steering Committee that Ancillary Study submissions be encouraged from Investigators outside the 7 Clinical Centers. This creates some problems with logistics and IRB approvals that are considered below. In general the same processes for application will apply, but the following points will need clarification in a separate page from the External Ancillary Investigator.

__ Will this ancillary study proposal work 1) independently of the existing CRIC consortium, 2) with an existing clinical center or centers, or 3) only with the SDCC?

__ Does this proposed ancillary study involve direct contact with research subjects by investigators outside the 7 clinical centers?

__ Does the local IRB forbid or restrict investigator access to an existing study without de novo submission to the IRB of a full protocol detailing the project? Are such restrictions limited to direct contact, or do they also apply to stored demographic data and biologic samples?

__ Will the proposal bring resources or expertise outside of those already available?