# CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION CLINICAL TRIALS (CKD-EPI CT)

# ORGANIZATIONAL STUCTURE AND PUBLICATIONS, PRESENTATIONS, AND ANCILLARY STUDIES POLICY

**APRIL 2, 2020**

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## SECTION A. ORGANIZATIONAL STRUCTURE

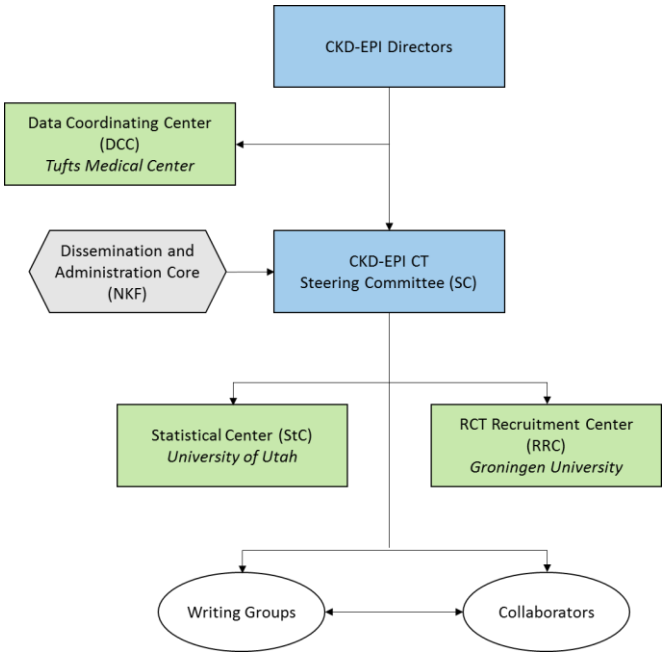
The CKD Epidemiology Collaboration (CKD-EPI) is a research group with major interests in measurement and estimation of GFR (CKD-EPI GFR)[1-3] and evaluation of surrogate endpoints for clinical trials (CKD-EPI CT)[4-12].

The organization for the CKD-EPI CT is modeled after that used for the CKD-EPI GFR and the CKD Prognosis Consortium (CKD-PC).[13,14] CKD-EPI CT includes analyses of randomized controlled trials (RCTs) and other studies initially collected for the purposes of evaluation of surrogate endpoints. Future analyses may go beyond the evaluation of surrogate endpoints but datasets will be restricted to RCTs (herein referred to as studies).

### A1. Organization

Figure 1 shows the organizational chart. CKD-EPI directors are Andrew S Levey MD and Lesley A Inker MD MS. The Data Coordinating Center (DCC) for CKD-EPI is at Tufts Medical Center, under the direction of Dr Inker. The steering committee (SC) for CKD-EPI CT will guide the overall direction and policies specifically for the work on surrogate endpoints, and will be chaired by Dr. Inker. The statistical center (SCC) is at University of Utah is under the direction of Tom Greene PhD. RCT Identification and Acquisition Center is at Groningen University under the direction of Hiddo L. Heerspink PhD. The steering committee will consistent of permanent members, one representative of CKD-PC, and 3-4 rotating members. Permanent members of the steering committee are Drs. Inker, Greene, Heerspink and Levey. CKD-PC representative will be decided upon by CKD-PC. Rotating members will rotate every year and will consist of collaborators, representation from industry, regulatory agencies, thought leaders or methods experts in this scientific field, or other organizations involved in the analytical questions.

**Figure 1: Organizational Diagram**



**A2. Studies included in CKD-EPI CT and methods of analyzing individual studies**

- CKD-EPI CT studies have been identified through systematic searches conducted in 2007 2016, 2017 and 2018. The ongoing goal is to include additional RCTs on a rolling basis as they become available. Key inclusion criteria are quantifiable measurements of albuminuria or proteinuria or serum creatinine to estimate GFR at baseline, measurements of serum creatinine in follow-up to estimate GFR decline and information on ESKD incidence thereafter. The number of ESKD events required varied by disease. Our previous publications describe the process of the literature search and study identification and acquisition in detail.[5,6,11,15,16]
- Each study has a primary collaborator who serves as point of communication to other collaborators or the study steering committee
- Collaborators are able to opt-in or opt-out of all analyses and publications based on their availability of data and willingness to contribute.
- We encourage cohorts to send de-identified individual participant level data to the DCC and StC as this reduces improves flexibility of analyses as well as reduced the burden on individual study analytical teams. As a second line, we are able to analyze the code on a shared server but is time inefficient and slows down the process tremendously especially if required to do across many studies. As a third line option, we are in the process of developing code to send out to the individual studies recognizing this will limit flexibility of refining and updating the analyses.

**A3. Roles and Responsibilities**

- Steering committee
  - Have overall responsibility for the direction of CKD-EPI CT
  - Identify and secure funding
  - Determine topics for analyses. Analyses will be rolled out in phases, where each phase identifies one or more papers that can be completed over 12-18-month period.
  - Review ancillary study requests from other investigators
  - Review other requests from industry or individuals for specific analyses to be done
  - Assigns writing group members

- DCC
  - Literature search, communication with collaborators to identify studies, data use agreements, data transmission, data cleaning
  - Analyses of pooled datasets
  - Coordination of manuscripts
  - The DCC will keep track of volunteering investigators and those investigators submitting proposals for all ancillary studies.
- Statistical Core
  - Develop methods for new analyses
  - Establish QC methods for new and established methods
  - Advise DCC on analyses
  - Coordinate communication of methods for publications and result presentations; and addressing any related questions
  - Coordinate any power or sample size related questions
- RCT identification and acquisition Center
  - Coordinate efforts with DCC to engage with potential volunteering investigators and gain access to study data

## SECTION B. SELECTION OF TOPICS FOR ANALYSES

**Main topics:** The steering committee will vet main topics based scientific interest, results of survey of collaborators for priority topics, and other factors. These can be divided into primary and secondary topics. Writing group for primary topics will be restricted to steering committee, DCC, Stc and RCC members, and collaborators. Writing group for secondary topics could include other interested parties, especially with content expertise.

**Ancillary topics** include those not specified in this analysis plan, but using CKD-EPI CT data and require additional funding to the DCC to fund the analyses. If these analyses lead to manuscripts, the writing groups can be composed of the investigators proposing the ancillary topics, collaborators and potentially member of the DCC, StC and RCC, depending upon the topic and technical resources required.

All collaborators will have the opportunity to opt in or opt out of every analysis

## SECTION C: PUBLICATIONS AND PRESENTATIONS POLICY

### C1 Dissemination of Results and Confidentiality

We plan to disseminate the final results to the general public through peer reviewed publications and presentations at scientific conferences. In advance of this, we anticipate sharing the results with Consortium members through several methods which might include those outlined below. For items 1-3, we would request signed confidentiality agreement with consortium members. For items 4, we will follow author criteria as outlined in the publication policy below.

1) Preliminary analyses for internal discussion
    - Marked strictly confidential – not to be shared outside this consortium and not appropriate for presentation to regulatory agencies
2) QCed specialized analyses
    - Can be presented to regulatory agencies
    - Shared across consortium, but not outside
3) Referenceable online report which is updated periodically that includes
    - Input data for power calculations
    - Updates to meta-analyses of treatment effects on each endpoint
    - Updates of trial level meta-regressions as new studies are added to the data base
    - Requires extensive resources and agreement by those who provide the data to us; assumes continued funding above current level
4) Referenceable peer reviewed publications and presentations at scientific conferences

### C2. Authorship

All publications from the CKD-EPI CT follow approved authorship formats. All manuscripts will be written by a writing committee, with initial drafts by first and last authors and DCC. All

collaborators of the CKD-EPI CT whose data were included in a manuscript may participate in writing committees. SC and DCC members may participate as appointed by SC. All authors and collaborators have full access to the results from all analyses. Other collaborators (up to 4 per study in addition to the author) will be acknowledged in the manuscript as CKD-EPI CT collaborators. Subject to specific journal policies, the goal is to have CKD-EPI CT collaborators indexed in PubMed.

All abstracts and manuscripts from the CKD-EPI CT will be prepared and submitted by writing committees. All authors are expected to review all manuscripts. Manuscripts will also be sent to the CKD-EPI CT collaborators who are not included in the writing groups, from whom data have been used for the analyses, for review and comment.

**C3. Formation of Writing Committees**

***Main topics***

The DCC will send out a questionnaire inviting volunteers for writing groups for the set of papers that emanate from an analytical phase. All CKD-EPI CT collaborators who contributed data to a specific manuscript may volunteer to participate in the writing committee for each paper. SC, DCC, StC and RCC members' interest will also be elicited. Writing groups for secondary topics can also include other interested parties, such as statisticians engaged in the research area or investigators with experience in this topic. The DCC will compile the list of volunteering investigators and will review with the SC, who has the final authority on the composition of the writing committee. If there are more volunteers than able for a particular study, we will give consideration primarily to those with submitted their requests first, but also with consideration to those investigators with prior work or publications in the field.

In general, one collaborator per study will be assigned to one paper from a set of papers that emanate from an analytical phase. For example, if three papers come from one analytical phase, no more than one collaborator from each study will be included in one of the three writing groups, but up to four collaborators from each study will be listed in the back and indexed in PubMed where possible.

The SC will assign the first or last author of the writing committee and its members. The exception will be if a paper highlights selected studies, then one collaborator from each of those studies will be included even if they or other collaborators from that study are already participating in a writing group.

***Ancillary topics***

CKD-EPI CT collaborators may submit written proposals to the SC, as detailed in the Ancillary Studies Policy (Section D).

If approved, the "proposer" of the ancillary manuscript shall be the chair of the writing committee, unless decided otherwise by the SC. Reasons for a change will be discussed with the proposer prior to a decision. The DCC will notify CKD-EPI CT collaborators, who may volunteer to participate in the writing committee.

The DCC will assign the other members of the writing committee, after discussion with the chair, and based on the volunteers.

A more detailed description of the formation of writing committees and the procedure to submit proposals for ancillary studies is given in Section D4 of this document.

***Authorship format***

Writing committee members will be listed as authors in the front page. The SC chooses the first and last authors based on the volunteers. In general, our philosophy is that credit should correspond to work and effort into a particular manuscript and the order of authors should reflect that. The base scenario for author order is first author, second author if this has been specified, the DCC members, alphabetical listing of the collaborating trial representatives, alphabetical listing of other members of the SC if appropriate, and the last author, however this will be modified depending on work contributed. "The Chronic Kidney Disease Epidemiology Collaboration" could be chosen as sole author or as last author.

CKD-EPI CT collaborators are listed in the acknowledgements. Editors of journals / PubMed will be requested to index all collaborators individually. In general, there is a maximum of 4 collaborators per collaborating trial (including members of the writing committee) and this can all be acknowledged in the manuscript.

***Acknowledging funding of individual studies***

A list of the key grants supporting the data collection in the individual cohorts will be included in manuscripts, either in the main paper or as web appendix.

**C4. Manuscript Generation and Review**

The same rules apply to all manuscripts.

**Main papers** will be written by the first and last author for each topic, with the methods section drafted by the DCC and StC. The DCC will develop, tables, and figures for review by the first and last author and will work together to finalize a draft for review by the Writing Group.

**Ancillary papers** will be similar to the main papers but there will be additional responsibility for the overall design and methods of the paper for the Ancillary study PI.

**C5. Abstract Generation and Review**

The same rules apply to abstracts about main and ancillary topics.

Approved writing committees may submit abstracts to national and international meetings, in accordance with rules governing the meeting.

Completed abstracts will be subject to review by the SC and will be sent to collaborators, from whom data have been used for the analyses, for comment.

Abstracts cannot be submitted for publication without approval of the SC. The goal will be to approve drafts within 1-2 weeks.

### C6. Presentations

Use of unpublished meta-analyzed data (including analyzed data of individual studies as a form of forest plots or tables with similar concept) for presentations will be limited and need prior approval by the SC. Acceptable reasons to present unpublished meta-analyzed data are (1) the use for other scientific workgroups, where gain is mutual to CKD-EPI CT and materials are kept to within the group, (2) Official CKD-EPI CT presentation where showing upcoming progress is important for CKD-EPI CT funding/continuation, (3) presentation by the writing group of submitted abstract. Reviews/invited talks should focus on materials published or in press. Key presentations of CKD-EPI CT meta-analyzed data will be made available on the CKD-EPI website for use by all collaborators.

### C7. Abstract/Manuscript Submission

Unless otherwise specified and agreed upon, DCC will submit abstracts and manuscripts on behalf of the writing groups.

The corresponding author for all CKD-EPI CT manuscript submissions will be listed as follows:

> "Chronic Kidney Disease Epidemiology Collaboration Data Coordinating Center (Principal Investigator, Lesley Inker, MD, MS), Division of Nephrology, Tufts Medical Center, 800 Washington Street, Box 391, Boston, MA 02111 Tel: 617-636-2569 linker@tuftsmedicalcenter.org"

CKD-EPI will pay or reimburse for the submission fees and publication cost of CKD-EPI CT abstracts and manuscripts but not ancillary studies.

## SECTION D. ANCILLARY STUDIES POLICY

### D1. General Policy

We welcome proposals for ancillary studies from investigators and collaborators in CKD-EPI CT. Ancillary studies can enhance the value of CKD-EPI CT and encourage interest of the overall goals. Nevertheless, to protect the integrity of CKD-EPI CT and ensure adequate resources, such ancillary studies must be reviewed and approved by the SC before their inception. Ancillary studies require outside (non-CKD-EPI) funding to support coordination and statistical analyses.

### D2. Definition of an Ancillary Study

An ancillary study is a proposal for an investigation using data submitted to the CKD-EPI CT which is not in the original CKD-EPI CT analysis plan. It is anticipated that proposals for ancillary studies cannot be supported by the presently available funding of the CKD-EPI CT. Ancillary studies should therefore have additional funding. At this time, only CKD-EPI collaborators can submit proposals for ancillary studies.

**D3. Requirements for Approval of an Ancillary Study**

The proposal must be in writing using standard scientific investigation format. Before an ancillary study can be approved, it must be shown to have scientific merit and that it will not do any of the following:

1. Interfere with the completion of the main objectives of CKD-EPI CT
2. Adversely affect collaborator cooperation in CKD-EPI CT
3. Create a diversion of study resources (personnel, equipment, or study samples), neither locally nor centrally, and
4. Jeopardize the public image of CKD-EPI CT.

**D4. Preparation of Request for Approval of an Ancillary Study**

The CKD-EPI CT will utilize a two-step process for reviewing ancillary study proposals. Step 1 involves the submission of a brief description of the ancillary study for "concept approval". Step 2 requires the submission of a more complete technical proposal. Submission materials must be in an electronic format.

Step 1: Letter of Intent: Submit a request for concept approval to the CKD-EPI Steering Committee. Include a brief (2-4 page) description of the proposed ancillary study that specifies:

1. Identification of the principal investigator of the ancillary study
2. Names of definite or possible co-investigators/collaborators (consideration of collaborating with the existing DCC and StC strongly urged)
3. Description of objectives/specific aims
4. Scientific merit of the study
5. Study design and timeline
6. Methodology for new data collection and indication of what existing data will be needed
7. Who will conduct data analysis? Refer to Section C8.
8. Proposed funding sources
9. Discussion of impact on CKD-EPI CT investigators and collaborators
10. Agreement that all ancillary data (clinical information, laboratory assay results) will be shared with the CKD-EPICT Data Coordinating Center.
11. Agreement to follow CKD-EPI CT publications policy for ancillary topics

Step 2: Ancillary Study Proposal: If concept approval is granted, the Steering Committee will invite the Principal Investigator to submit a complete proposal. Approval of the technical proposal is required prior to submission to the funding agency or study initiation. The proposal should be submitted to the Steering Committee and should include the items listed below. Items 1-5 can be include as part of the submitted grant application.

1. Description of objectives/specific aims
2. Scientific merit of the study
3. Study design and hypotheses
4. Methodology for data collection
5. Power calculations (if appropriate) and proposed statistical analyses
6. Identification of principal investigator of the ancillary study
7. Names of definite or possible co-investigators/collaborators (consideration of collaborating with the existing DCC and StC is strongly urged)

8. Proposed funding sources
9. Budget for data coordination, if applicable.
10. Budget for laboratory coordination, if applicable
11. Budget for statistical analysis.
12. Agreement that all ancillary data (clinical information, laboratory assay results) will be shared with the CKD-EPI CT DCC.
13. Agreement to follow CKD-EPI CT Publications Policy for ancillary topics.
15. Proposed authorship format and the intended journal.

**D5. Review of Ancillary Study Proposals**

Proposals will be sent to the Steering Committee for review, who may confer with collaborators with expertise on the topic. The Steering Committee will approve, reject, or request modification of the ancillary study proposal. The key criteria for approval of proposals are scientific merit and impact on the main CKD-EPI goals. If the ancillary study is approved by the CKD-EPI Steering Committee, the Chair of the Steering Committee will write a letter to the principal investigator of the ancillary study indicating approval and support of CKD- EPI Steering Committee. This letter can be used to document approval and support in submission of grant applications for funding or local IRB approval. If the Steering Committee does not provide approval, the proposal will be rejected.

**D6. Selection of Investigators/Collaborators in Ancillary Studies**

If concept approval is indicated by the Steering Committee, the DCC will circulate a notice with a request for CKD- EPI CT collaborators, in addition to those submitting the proposal, to participate in the ancillary study (opt-in / opt-out procedure), which CKD- EPI CT collaborators would like to be part of the writing committee (investigator) and whether there are comments / suggestions. CKD- EPI CT collaborators must volunteer in writing (electronically) to the Steering Committee. The Steering Committee will compile the list of volunteering investigators. If there are more volunteers than necessary, approval for collaboration will favor those investigators with prior work or publications in the field. The Steering Committee shall have final authority on the composition of the ancillary study investigators. The Data Coordinating Center will keep track of volunteering investigators and those investigators submitting proposals for all ancillary studies.

**D7. Progress Reports**

The Principal Investigator shall provide a written annual report on the progress of the ancillary study. Based on progress achieved, the Steering Committee will recommend approval or disapproval for continuation of the ancillary study. In the case of disapproval, permission to continue the ancillary study may be granted to another co-investigator/collaborator (subject to approval by the funding agency).

**D8. Analysis of Ancillary Studies**

The investigator of the ancillary study, and if necessary the Steering Committee, will consult with the DCC and StC 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. In general, the IPD of participating cohorts is provided to the DCC for analysis without permission for transfer to other places. Therefore arrangements will need to be made to fund analysts or access the data at the

DCC. The investigator of the ancillary study will receive analyzed results, but not IPD, from the DCC.

**D9. Publications from Ancillary Studies**

Publications from ancillary studies shall follow the CKD-PC Publication Policies related to ancillary topics.

## SECTION E. POLICY ON INDIVIDUAL TRIAL PUBLICATION

This Scientific Workshop is based on the mutual interest of all trials to participate in collaborative research that will improve our understanding and use of alternative endpoints in trials of kidney disease progression. The CKD-EPI CT encourages the activity of individual trials. The publications from individual trials are beneficial to science and the collaboration as a whole.

In the event that there is future funding for CKD-EPI CT to pursue more investigations on these topics, the experience and expertise of collaborating trials will be helpful when CKD-EPI CT pursues similar topics. We will use the term “vanguard papers” for such projects which aim to improve and refine future CKD-EPI CT projects.

If authors believe they have gotten ideas from CKD-EPI CT work (e.g., study design, statistical code) and deem it appropriate to do so, acknowledgement of the collaboration would be appreciated. The DCC aims to continue to share methods and expertise and respond to requests by individual cohorts as much as possible.

While the consortium generally encourages individual trials publishing, groups forming small multi-trial collaborations may not be beneficial for the consortium. This is particularly the case for topics that are being discussed for a full meta-analysis in the consortium. CKD-EPI CT encourages collaborators thinking to form a small collaboration to consider the possibility to proceed with their projects in the entire consortium whenever possible.

## SECTION F. POLICY ON INDUSTRY AND INVESTIGATOR REQUESTS FOR ANALYSES IN SUPPORT OF STUDY DESIGN

The datasets included in CKD-EPI CT are a tremendous source of potential information for study design such as power calculations, event rate estimations, and other questions. Since the goal of this consortium is to provide evidence to support study design, our goal would be to provide publically available summary data that can be used widely. This information will help to translate the methodological investigations of the optimal endpoints to real-world study design

- All requests for specific descriptive data to support development of study designs by individual investigators or sponsors will require approval by the steering committee.
- To be approved, analyses in support of specific study designs must be generally applicable to other work of the consortium. The results of all these analyses will either be made available to consortium members on the CKD-EPI CT password protected page of the NKF website or, if appropriate, will be made publically available on the CKD-EPI.org website.
- Summary data will ultimately be included in supplementary tables of published manuscripts and prior to that will be available on the CKD-EPI CT password protected page of the NKF or the CKD-EPI.org website. Collaborators will have a chance to review data prior to posting or publication
- Data shared with consortium members intended for confidential use only, ie that are not on a publically available website or published cannot be used for any purpose (e.g but not restrictive to presentation to the FDA, EMA or other regulatory agencies, presentation at the ASN or other forums, or publication). A confidentiality agreement must be signed renewed yearly before consortium members can participate in webinars and have access to the shared private website. Members who wish to use these data for presentation at private meetings such as with regulatory agencies must request permission from the CKD-EPI CT Director who will then review with the steering committee

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