

Pilot Clinical Trials in CKD Manual of Operations Revision of 10/31/2017		
Chapter #	General Chapters	Revision Date
3	Publications and Presentations Policies	07/02/2015
4	Ancillary Studies	03/11/2014
6	Event Review System	05/25/2016
7	Clinical Site Set-Up and Management	
	Investigator Study Team Face-to-Face Meeting Log	03/05/2015
	Appendix 1: Early steps in setting up a Pilot Clinical Trials in CKD Clinical Center	06/24/2014
8	Forms Completion, Data Entry and Data Discrepancy Resolution	04/19/2017
9	Data and Lab Quality Control	
	Appendix 1: CKD Study eGFR Equation	05/12/2016
	Appendix 2: BSA formula	05/12/2016
11	General Recruitment Issues and Strategies	03/30/2015
	Appendix 1: Study Participant Information	11/13/2014
Chapter #	BASE Study Chapters	Revision Date
30	BASE Study Overview and General Information	
	Appendix 1: Items to have on hand when BASE Study starts	05/12/2016
	Appendix 2: Reasons Candidates Approached for BASE but Did Not Consent	10/08/2015
31	Managing BASE Study Participants	02/16/2017
	Appendix 1: Listing of Common PPIs and H2 Blockers	12/30/2015
	Appendix 2: List of Common ACEI and ARBs	02/09/2016
32	BASE Study Participant Educational Materials	01/07/2016
	Sodium Handout - BASE	
33	BASE Laboratories Overview	04/12/2016
	Appendix 1: Specimens Collection and Shipping Guide	05/11/2015
34	BASE Study Litholink Central Lab	11/10/2016
	Appendix 1: Material Safety Data Sheet – Preservative	05/30/2006
	Appendix 2: 24 Hour Urine Collection Kit Procedures	04/02/2015
	Appendix 3: Litholink Supply Order Form	09/21/2015
35	NIDDK Biorepository for BASE Study Samples	10/02/2015
	Appendix 2: NIDDK Biorepository Kit Re-Order Form	02/16/2016
36	BASE Study Anthropometry Ankle Measurement	01/30/2017
	BASE Study Anthropometry Ankle Measurement PowerPoint	03/15/2015
	Handouts - BASE	
	24-Hour Urine Collection Instructions (female) – BASE template	12/22/2014
	24-Hour Urine Collection Instructions (male) – BASE template	12/22/2014

Chapter #	COMBINE Study Chapters	Revision Date
50	COMBINE Study Overview and General Information	05/12/2016
	Appendix 1: Items to have on hand when the COMBINE study starts	01/16/2015
	Appendix 2: Reasons Candidates Approached for COMBINE but Did Not Consent	05/21/2015
	Appendix 3: Reasons Some Candidates Were Not Approached	12/22/2014
51	Managing COMBINE Study Participants	08/03/2016
	Appendix 1: Participant Re-enroll Flowchart	04/01/2015
52	COMBINE Participant Dietary Educational Materials	
	Dietary Phosphorus Quick Start	V1.0
	Fast Food Choices: Better vs. Poor Choices	V1.0
	Fast Food Restaurants: Phosphorus Found in Foods	V1.0
	Fast Food Restaurants: Better Choices	V1.0
	Food Smart: Understanding Food Labels	V1.0
	Overview for Physicians Letter	V1.0
	Overview for Participants Brochure	V1.0
	Your Plate: Fruits, Vegetables, Protein and Grain Portions	V1.0
	Pre-Enrollment Recruitment Telephone Script	V1.0
	Smart Snacks	V1.0
	Food Products Commonly Containing Phosphorus Additives	V1.0
	Hidden Phosphorus in the Diet	V1.0
53	COMBINE Laboratories Overview	
	Video: Overview of Laboratory Collection, Processing and Shipping Procedures	03/25/2015
	Appendix 1: Specimens Collection and Shipping Guide	01/13/2015
54	COMBINE Study Spectra Central Laboratory	09/07/2016
	Appendix 1-Adding Acid to Urine Containers	10/20/2015
	Appendix 2-Spectra Critical Lab Values for Randomized Participants	10/31/2017
	Spectra Supply Reorder Form	06/13/2017
	Spectra 24-Hr Urine Collection Participant Instructions	V1.0
	Hydrochloric Acid Information Sheet	05/25/2016
55	UW FGF23 Core Laboratory Manual	06/22/2015
56	Cardiac and Renal MRI Core Laboratory	02/26/2015
	Appendix 1: CTI Safety Questionnaire	06/10/2014
	Appendix 2: MRI Appointment Reminder and Instructions	10/01/2014
57	NIDDK Biorepository for the COMBINE Study	03/03/2015
	Appendix 1: NIDDK Biorepository Supply Reorder Form	06/17/2015
58	Drug Distribution Center	
	Material Safety Data Sheet – Endur-amide	09/03/2014
	Material Safety Data Sheet – Lanthanum Carbonate	01/2007
	Ingredient Listing for Placebo for Endur-amide	08/22/2014

Chapter #	TarGut Microbiome Study Chapters	Revision Date
	Interviewer instructions for starting a new FFQ session	12/18/2014

CHAPTER 3: PUBLICATIONS AND PRESENTATIONS POLICY

3.1 Group Definitions

CKD Study Investigators

For the purposes of this policy, *CKD Study Investigators* are all individuals affiliated with the CKD Study to whom this policy will apply. The *CKD Study Investigators* are categorized into three groups:

- 1) CKD Study PIs
 - a) CKD Study Principal Investigators at the Clinical Centers and Data Coordinating Center
 - b) NIDDK Project Scientist
 - c) Steering Committee Chair
- 2) CKD Study Investigators
 - a) Typically, investigators who are at the Clinical Centers, Data Coordinating Center and Central Cores, other than *CKD Study Principal Investigators*.
 - b) Research staff and study coordinators
- 3) Ancillary Study Investigators
 - a) Individuals who propose, receive approval from the PAS Committee, and obtain funding for a CKD ancillary study.

Publications and Ancillary Studies (PAS) Committee

The CKD PAS Committee will be chaired by the Steering Committee Chair. Other members are the CKD Study voting Steering Committee members, or alternative designee from each site.

3.2 Publication Policy Principles

- 1) Publication of scientific research papers is a central and critical aspect of each CKD Study because:
 - a) Scientific publications will be the principal mechanism by which each CKD Study will communicate its scientific findings.
 - b) Scientific publications represent one of the most important mechanisms for CKD Study Investigators to achieve scientific and academic recognition for their participation in CKD Study.
- 2) Research questions and hypotheses to be addressed using CKD Study data should be formulated *a priori* and clearly stated in a manuscript.
- 3) Publication policies should promote scientific inquiry within and productivity from the CKD Study.
- 4) To avoid premature publication of results that might compromise the performance of the study (such as by publication of trends of results before such trends become statistically convincing) or that might compromise the ability to publish the results in high-quality peer-reviewed journals (as by premature release to the lay press).
- 5) Publication of scientific findings from each CKD Study should proceed in a timely fashion once relevant analyses are complete.
- 6) Abstracts, presentations, and publications based on CKD Study material must be accurate and objective and must not compromise the scientific integrity of Study.
- 7) The publications arising from each CKD Study should avoid overlap (except for review articles) and conflicting representation of Study findings.

- 8) Recognition through authorship will be distributed among the *CKD Study Investigators* so that:
 - a) *CKD Study PIs* have equitable opportunity to lead and co-author CKD Study publications.
 - b) *CKD Study Investigators* have opportunity to lead and be co-authors on publications resulting from analyses made possible through their collaboration, and participate in publications reporting scientific findings to which they have contributed.
 - c) *Ancillary Study Investigators* have the opportunity to lead and be co-authors on publications resulting from analyses made possible through their collaboration.
- 9) The CKD Study promotes the career development of junior faculty by providing them opportunity to lead and to be recognized as co-authors of CKD Study publications, as appropriate.
- 10) Authorship on CKD Study publications will adhere to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors.

To adhere to these principles, it is the policy of the Study that preparation of all publications or presentations, other than materials prepared for local publicity purposes (see Section 23.3), must be assigned by the Chair of the Publications and Ancillary Studies (PAS) Committee to specifically appointed writing committees. Materials must be reviewed and approved by the PAS Committee and/or the Steering Committee before publication or presentation.

3.3 Scope of Policy, and Exception for Local Informational Materials

All material to be presented orally, as poster, or submitted for publication for dissemination by individuals associated with the Study and dealing with any aspect of the Study must receive prior review and approval by the PAS Committee with the following exception:

Material prepared for informational purposes within the recruitment region of a CKD Clinical Center, or presented orally or as handouts or posters to local professional audiences solely for the purposes of informing the profession of the Study and its objectives, need not be reviewed by the PAS Committee. Such material must be limited to a background discussion of chronic kidney disease treatment and a description of the Study organization, objectives, and entrance criteria, and to results of the Study that have previously been presented to a scientific body or published in a scientific journal. It must not include discussion of any study data not previously presented or published. Informational material for national dissemination, including lay summaries, does need to be reviewed and approved by the PAS Committee.

3.4 Source of Suggestions for Publications of the Study

Suggestions for topics appropriate for preparation of abstracts or peer-reviewed papers are made by the PAS Committee. In addition, all investigators and staff in the Study are invited to suggest topics appropriate for preparation as abstracts and peer-reviewed papers from the Study. Such suggestions should be made to the DCC and the Chair of the PAS Committee, who shall review the request to be certain that there is no overlap with materials previously assigned, or planning to be assigned, to other writing committees. Where such overlap exists, the Chair of the PAS Committee may make recommendations that the suggestion be referred to an existing writing committee, that additional study investigators be added to existing writing committees, or make other suggestions to resolve the overlap. However, final decision in this matter will be made by the Chair of the PAS Committee.

It is the intent of this policy to encourage non-physician professionals to prepare scientific presentations to their own professional meetings and to prepare scientific papers for their own professional journals in addition to participating in the preparation of papers for medical journals. Since the subject matter of these reports and papers may well overlap with material being prepared by writing committees for medical journals, it is the policy of the Study that under these circumstances, rather than forming a new writing committee, such non-physician professionals should be added to the existing writing committee concerned with related matters, specifically for the purposes of preparing such reports. The authors of these presentations and reports will be the members of the writing committee, with first author being the individual added to the committee for this purpose, using the appropriate authorship style described in Section 23.7.

It is also the intention of this policy to promote the conversion of as many abstracts as possible into full manuscripts and to discourage the production and presentation of abstracts that do not represent an intermediate step towards the preparation of a full scientific manuscript.

In addition, the PAS Committee will formulate and maintain a list of suggested topics that should be prepared for publication, to assure that all completed aspects of the work of the Study are reported to the scientific community in a timely fashion.

3.5 Assignment of Writing Committees

Topics suggested for presentation or for publication that do not overlap with an existing committee will be circulated to CKD Study PIs and CKD Study investigators. Writing committees should be formed with the intent of writing a paper for publication. This committee can also prepare abstracts for submission to professional meetings. Volunteers for the writing committee solicited are from all investigators. Persons are requested to suggest and justify names for lead authors (Chair of writing committees) and co-authors. This information will be collated and reviewed by the Chair of the PAS Committee and the DCC PI. The Chair of the PAS Committee will decide on the final composition of the writing committee.

If a topic is suggested by an investigator of the Study, and approved by the PAS, the writing committee will be formed as just described and the person making the suggestion will be considered as the potential lead author. The Principal Investigator of an ancillary study should be considered for lead author of material derived from that ancillary study. If only a subset of clinical centers participate in an ancillary study, only investigators from these centers should be considered to be on writing committees relating to this study.

Appointments of writing committee chairs will be made fairly to all professionals -- physicians, study coordinators, nurses, statisticians, and others -- in a manner that recognizes the unique contributions of each member of the Study to its performance. Any dispute about the selection of the lead author or co-author will be settled by the Chair of the PAS Committee. In all cases, writing committees requiring analysis of data by the Data Coordinating Center will have at least one member of the DCC assigned to it.

From time to time it may be expedient for the chairmanship of a writing committee to be reassigned to another member of that committee, or for members to be dropped from or added to a writing committee. The Chair of the PAS Committee is authorized to make such changes with the consensus of the members of the writing committee, or on his own authority where there is clear cause.

3.6 Classes of Reports of the Study

There are four types of reports of each CKD Study:

- A. Reports of the major outcomes of each CKD Study.
- B. Reports addressing in detail one aspect of the Study, but in which the data are derived from the entire study.
- C. Reports of data derived from a subset of centers by members of the Study (e.g., substudies or ancillary studies), or originally conceived analyses of data from the entire Study (original analyses).
- D. Reports of investigations initiated outside the Study, but using data or samples collected by the Study. The investigators may be CKD or other investigators, but the source of the ideas and the funding for the study will have been derived outside the Study itself. Writing committees for this type are formed and presentations and publications made in accordance with the general policy rules for CKD publications. However, the Principal Investigator of an ancillary study should be assigned the prerogative and should take primary responsibility in publishing the results of the study.

3.7 Authorship Policy

The authorship policy of the Study must achieve two somewhat conflicting goals. First, it is recognized that the findings of the study, especially the findings reported in Type A and B reports, are derived from the efforts of the entire CKD professional staff. Thus, reports of Types A and B must give recognition to all the investigators of the Study, and other Types must give primary recognition to those participating in the specific investigation. On the other hand, it is recognized that the preparation of a manuscript places special demands on the assigned writing committee, and especially on the Chair of the writing committee. Further, recognition of special effort and achievement is important in the professional careers of the study staff, and specific listing as an author is a significant motivating factor that will help assure prompt completion of writing assignments and timely publication of the results of the Study. The CKD authorship policy attempts to recognize each of these goals. The authors of CKD Study publications will be listed as detailed below for each type of publication.

Type A publications:

Abstracts: [*specific study name*, e.g., The CKD Optimal Management with BInders and Nicotinamide (COMBINE)] Study Group¹, presented by XXXX.

Papers: [*specific study name*, e.g., The CKD Optimal Management with BInders and Nicotinamide (COMBINE)] Study Group¹, prepared by XXXX.

¹The CKD participant box, detailed below, must be included in these papers. If a society's or journal's policy does not allow authorship by a group, the authors will be listed first as in Type B publications.

Type B publications:

Abstracts and papers: Authors' names, and [*specific study name*, e.g., The CKD Optimal Management with BInders and Nicotinamide (COMBINE)] Study Group¹

¹The *specific study* participant box will be included in all papers if this can be arranged with the publisher. Otherwise it will be referenced to one of the Type A papers. It will not be practical to publish the entire list of participants in abstracts.

Type C and Type D publications:

Abstracts and papers: authors' names for [*specific study name*, e.g., The CKD Optimal Management with BInders and Nicotinamide (COMBINE)] Study

¹The participant box will be included in all Type C papers if this can be arranged with the publisher. Otherwise it will be referenced to one of the Type A papers. In Type D papers, the list of research personnel will be referenced in all cases. It will not be practical to publish the entire list of participants in abstracts.

3.8 Listing of Professional Participants in the Participant Box

The CKD Study participant box will list all professionals who have participated in the Study for a minimum of one year. The participants for each participating center will be listed together, with the center Principal Investigator listed first, and identified as "P.I." followed by the other center or investigators listed alphabetically. Each participant will be listed only by his/her professional and academic degrees, not by the specific position that he/she held in the study. The centers will be listed in the following order:

- Steering Committee Chair
- Clinical Centers (in alphabetical order by center name)
- DCC
- Cores/Repositories
- NIDDK

Prior to the publication of any papers from the Study, each center will be asked to confirm and approve the listing of the personnel from that center in the Participant Box.

3.9 Acknowledgement of Support

Acknowledgement of grant support to be used in all papers reporting results of the Study. (In the case of ancillary studies, additional sources of support should be cited as appropriate).

The Study is supported by the Division of Kidney, Urologic and Hematologic Diseases of the National Institute of Diabetes and Digestive, and Kidney Diseases, NIH. Additional support is provided by the (list of any industrial or other support).

3.10 Schedule for Completion of Writing Assignments and Resolution of Overlaps among Writing Committees

At the time that a writing committee is constituted, the PAS Committee will establish a timetable for the completion of the writing assignment that takes into account deadlines for the publication, the amount of time that will be required for data analysis, the other commitments of the DCC, and the priority of the publication. The Chair of the Writing Committee should provide the Chair of the PAS Committee a general outline of the proposed publication within a month of receiving its assignment, to permit the PAS Committee to identify any overlap with the assignments of other writing committees, and to permit establishment of an appropriate timetable. Where overlaps of materials to be covered by different writing committees are detected, the Chair of the PAS Committee will attempt to resolve these informally with the chairs of the involved writing committees. In the event that this effort at mediation fails, the issue will be resolved by the Chair of the PAS Committee. The Chair of the PAS Committee will report at each meeting of the Steering Committee on the progress of the various writing committees.

3.11 Review of Abstracts and Presentations by the PAS Committee

To expedite review of abstracts, oral presentations, and any other material for which there is an explicit deadline for submission, the following procedure will be used:

1) The writing committee shall contact the Chair of the PAS Committee and the DCC P.I. should be contacted. The Chair (or designee) will name a subcommittee of two members of the PAS Committee to review the submitted material and will inform the submitter and this subcommittee of their appointment. The submitted material should be sent by the submitter directly to these two reviewers so as to reach them no fewer than seven (7) days prior to the deadline for submission.

2) The members of the subcommittee shall review the material and notify the Chair (or designee) of their approval or disapproval. If there is unanimous approval, the PAS Committee Chair (or designee) shall inform (through the DCC) the submitter that he/she has approval for the submission.

3) All materials submitted for approval in this fashion will be distributed, together with notice of the disposition, to all members of the PAS Committee.

Approval for submission of an abstract or oral presentation does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval in accordance with the above rules at least seven (7) days prior to the scheduled oral or poster presentation. Normally this review will be done by the same subcommittee of the PAS Committee that reviewed the initial abstract.

1) In the case of an oral presentation, an outline of the talk and a copy of any slides to be used must be submitted for review.

2) In case of a poster presentation, the content of the poster material must be submitted for review.

Also, if there is a meeting proceedings paper, the lead author must notify the PAS Chair at the time the abstract is proposed and receive approval for both abstract and the affiliated proceeding paper.

3.12 Review of Papers by the PAS Committee

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference (including book chapters and reviews), whether or not there is a deadline for submission, must be submitted to the DCC for distribution to and formal review by the entire PAS Committee. If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the Chair, PAS Committee, at least 14 days prior to the deadline, to permit such review. This review will be conducted as follows:

1) The Chair of the PAS Committee, shall appoint at least two primary reviewers, one of which must be a PAS Committee member, and one of whom may be any professional member of the Study Group with appropriate expertise. The Chair (through the DCC) shall distribute the material to all members of the PAS Committee. The two primary reviewers shall each prepare and send to the Chair a written critique of the submitted material for distribution to the entire PAS Committee. The PAS Committee will be given a deadline by which any comments or critiques must be received by the Chair of the PAS Committee.

2) The Chair of the PAS Committee may schedule a conference call of the PAS Committee, to review papers and other non-time critical materials as agenda items. The reviews of the panel members and any comments received from the center PIs will be distributed to the committee with the agenda. Alternatively, the Chair can decide if the review can be done by email input, rather than by conference call.

3) While discussion of the submitted paper(s) and other materials will be led by the two appointed reviewers, all members of the PAS Committee will be invited to participate and all shall vote on final disposition.

4) In keeping with medical editorial traditions, there are three possible dispositions: approval of the material as submitted (possibly with some recommendations for revision that do not require re-review), non-acceptance of the material as submitted but with recommendations to the authors for revisions and resubmission, and disapproval of the material.

5) The Chair of the PAS Committee shall be responsible (through the DCC) for communicating the decision of the Committee to the authors, together with a summary of suggestions for revision, if any.

6) In the event that editors of a scientific journal to which an approved CKD scientific manuscript is submitted suggest or require major revisions of the manuscript, the revised manuscript must be reviewed again by the PAS Committee prior to resubmission in the same manner as described above. Generally, the Chair will appoint the same reviewers who first read the paper to review the revision, and every effort will be made to expedite such repeat reviews.

3.13 Criteria for Review of Materials by the PAS Committee

All materials submitted to the PAS Committee will be reviewed for acceptability on two grounds:

1) Materials shall be evaluated for scientific accuracy, quality, importance, and style. The intent is to assure that all approved CKD materials reflect well on the Study.

2) Materials shall be reviewed to assure appropriateness of the content. The material shall be reviewed to assure that it conforms to the assignment to the writing committee, addressing satisfactorily the assigned topics and not encroaching on material assigned to other writing groups. In addition, the material shall be reviewed to assure that it does not divulge prematurely the outcomes or findings of the Study or compromise the eventual publication of CKD findings in high quality peer-reviewed journals. In this later regard, it must be remembered that publication of reports of more than 400 words are generally taken to constitute prior publication of a body of material and will generally preclude subsequent publication of the material in a peer reviewed journal.

3.14 Maintenance of Records of Publications and Presentations

The DCC will maintain a record of all publications and presentations of the CKD Study, separated into the following categories:

- 1) Peer-reviewed accepted or published papers in professional journals
- 2) Abstracts published in citable journals
- 3) Presentations at regional, national or international meetings

This listing will be updated at least every six months and will be distributed to the all investigators in the Study, together with copies of any scientific papers or abstracts published since the last update. This is intended to inform investigators of all study findings and to facilitate the updating of curricula vitae.

3.15 Acknowledgement and Acceptance of CKD Study Policies on Publications and Presentations by the Study Investigators

To assure that all investigators (the three groups defined in Section 23.1) involved with the Study are aware of the policies of the Study, and to minimize the possibilities of misunderstandings after initiation of the Study, each investigator (except vascular function personnel, sonographers) will be given a copy of this Chapter and will be asked to sign a Statement of Understanding Form (see next pages) listing the major provisions of the Chapter and attesting to his/her acceptance of these policies. The original of the signed Statement of Understanding Form should be returned to the DCC. A copy of the Chapter and their signed Statement of Understanding Form should be kept by each CKD investigator.

CHRONIC KIDNEY DISEASE STUDIES

Statement of Understanding of Policy Concerning Publications and Presentations

To assure that all professionals involved with the CKD Study know and understand the policies of the CKD Study regarding publications and presentations, and to preclude the possibilities of misunderstandings after initiation of the Study, each professional member will be given a copy of the Manual of Operations Section 23 detailing these policies and will be asked to sign this form attesting to his/her acceptance of these policies, which are summarized below.

I. Material Covered by These Policies

All material to be presented at meetings or submitted for publication or dissemination by individuals associated with each CKD Study and dealing with any aspect of the Study must receive prior review and approval by the Publications and Ancillary Studies (PAS) Committee with the following exception:

Material prepared for publicity purposes within the recruitment region of a CKD Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of each CKD Study and its objectives, need not be reviewed by the PAS Committee. Material for national dissemination does need to be reviewed and approved by the PAS Committee. Such material must be limited to a background discussion of the issue involved and a description of the specific CKD Study organization, objectives, and entrance criteria, and to results of the Study that have previously been presented to a scientific body or published in a scientific journal. It must not include discussion of any previously not presented or published CKD Study outcomes or results, and must not itself result in publication of an abstract or other citable professional reference.

II. Assignment of Writing Committees for Publications

The PAS Committee will solicit volunteers for each writing committee for abstracts and publications and make a recommendation on the writing committee and topic to the CKD Steering Committee Chair. The CKD PAS Chair will decide on the final composition and topic of the committee. All interested individuals will be given a chance to request appointment to the various writing committees, but the final appointments will be determined by the Chair of the PAS Committee.

III. Authorship

The CKD policies specify the authorship for each of the four different classes of publication or abstract (See Section 3.6 of the Manual of Operations). These policies are binding and must be followed in all publications derived from the CKD Study.

IV. Review of Abstracts

All abstracts must be reviewed and approved by the PAS Committee before being submitted (See Section 3.11 of the Manual of Operations). These abstracts must be delivered to the reviewers at least seven (7) days before the submission deadline to permit time for this review. Abstracts not approved in this fashion will be withdrawn by the CKD Study.

V. Review of Materials for Presentations

Approval for submission of an abstract does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval by members of the PAS Committee at least seven (7) days prior to the scheduled oral or poster presentation.

VI. Review of Papers

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PAS Committee for formal review by the entire Committee (see Section 3.12 in the Manual of Operations). If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the Chair of the PAS Committee at least 30 days prior to the deadline, to permit such review.

VII. Certification by CKD Study Participant

This is to certify that I have read the above statement of policies of the CKD Study with regard to publications and presentations, understand it, and agree to abide by it in matters of all publications and presentations derived from the CKD Study.

(Signature)

(Date)

(Print or Type Name and Institution)

CHAPTER 4: ANCILLARY STUDIES

4.1 Purpose

To enhance the value of the CKD Study, the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies in collaboration with the CKD Study investigators.

4.2 Definition of Ancillary Study

An ancillary study is one based on information, images or biospecimens from the CKD Study participants in an investigation that is relevant to, yet not described in the CKD Study protocol, and derives support from non-CKD Study funds. It is anticipated that a typical ancillary study will propose the collection of additional data not collected or analyzed as part of the CKD Study parent data set.

4.3 Ancillary Study Principles

- 1) Participation in, and approval of, an ancillary study is subject to review by the CKD Study Publications and Ancillary Studies (PAS) Committee. See Section 23.1 for composition of the PAS Committee. Also, the CKD Study Data, Safety and Monitoring Board is notified of all ancillary studies.
- 2) Approval by the PAS Committee will be defined as a majority of votes in favor of the proposal. In the case of an ancillary study which includes subject participation at all clinical centers, two-thirds approval of the PAS Committee membership will be required. Furthermore, the centers participating must each approve.
- 3) An ancillary study must receive PAS Committee approval before a grant to support it is submitted to a funding agency or to local institutional authorities (e.g., IRB), and before the study is permitted to begin.
- 4) All CKD ancillary study proposals initiated by a non-CKD investigator as PI must include as a Co-investigator at least one CKD Study PI or Co-investigator.
- 5) Ancillary studies require external (non-CKD Study) funding. Any ancillary study must have sufficient funding to cover the costs incurred by the CKD Study Clinical Centers and Cores (e.g., to process or ship samples), and the Data Coordinating Center (DCC) (for tasks such as sample selection, data management, preparing and documenting analysis files, participating in statistical analysis, and integrating the new ancillary data into the combined CKD Study database). Also, studies using Repository biospecimens must have adequate support for handling and using the specimens. Special consideration will be given to requests for ancillary studies to be funded through training grants or career development awards through the NIH or other peer-reviewed funding sources.
- 6) Considerations for approval of ancillary studies
The proposed study:

- a) must meet requirements of the highest scientific merit.
 - b) must not, or minimally, interfere with the completion of the main objectives of each CKD Study.
 - c) must not, or minimally, adversely affect participant cooperation or compliance with each CKD Study.
 - d) must not create a serious diversion of CKD Consortium Study resources.
 - e) must put minimal demand on scarce CKD Study Consortium resources, such as blood samples.
 - f) must require the unique characteristics of the CKD Study patient data to accomplish its goals.
 - g) must have adequate resources to effectively complete the project.
 - h) must agree to provide the ancillary data to the CKD Study Consortium (also see 10 and 11).
 - i) must not jeopardize the public image of the CKD Study Consortium.
 - j) consider using the entire cohort for testing, rather than individual centers or isolated subgroups when appropriate.
- 7) Once an ancillary study is approved, if a change occurs in the structure or concept of the study (for example as a result of the NIH review process), including any change in data elements to be collected or analyzed, or any change to study aims, such changes must be disclosed to the PAS Committee and the CKD Study Steering Committee, for review and approval before the proposal is (re-)submitted to a funding agency.
- 8) A written progress report on ancillary studies must be made periodically (e.g., at time of Steering Committee meetings) to the Steering Committee.
- 9) All data collected under the auspices of an ancillary study is expected to adhere to the same high standards of quality applied to data collected in the CKD Study Consortium. A plan for quality control must be submitted to the DCC for funded studies. In addition, once the ancillary study is initiated, periodic quality control reports must be sent to the DCC.
- 10) Data from ancillary studies will be made available to the DCC either on a real time basis using direct data entry into the DCC's computer server or through periodic (e.g., quarterly) transfers of ancillary data to the DCC.
- 11) An archival copy of the collected data and/or laboratory results not already held at the DCC will be sent to the CKD Study Data Coordinating Center at the conclusion of the data analysis and publication of the main ancillary study results. This transfer is the responsibility of the ancillary study CKD Study collaborator(s). Once transferred back to the CKD Study Consortium, these ancillary data will become part of the aggregate CKD Study data.
- 12) Images, tracings and biosamples may usually be kept by the ancillary study investigators. During the CKD Study operation, further use of the samples beyond the objectives that have been approved by the PAS is prohibited without additional

consent from the PAS Committee. The restrictions on specimens imposed by the Veterans Affairs for specimens collected at the VA sites must be observed. Also, the NIDDK has the option to require that the images, tracings (or copies of) and remaining biosamples be transferred to the NIDDK Repository at the end of the CKD Studies.

- 13) Unless specifically arranged, all analyses will take place at the DCC and be conducted under the supervision of its biostatistician-investigators in collaboration with the ancillary study investigators. Under specifically approved circumstances, datasets will be released to external investigators for local analysis.
- 14) Proposals for abstracts and manuscripts resulting from all ancillary studies shall be submitted to the PAS for review and approval 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.
- 15) Information about proposed ancillary studies, and progress and results from approved ancillary studies are considered to be confidential and are not to be shared with others outside of the CKD Study Consortium except as provided for by the CKD Study Publications and Ancillary Studies Policy. Ancillary study investigators can share information among their co-investigators and with CKD Study investigators.

4.4 Funding of Ancillary Studies

Ancillary studies will not be funded by the CKD Study, but will require an independent source of funding.

4.5 Approval Procedures

- 1) Proposals may be generated by a participating clinical center or by other interested investigators providing at least one CKD Study PI or Co-investigator is included as a co-investigator. These applications are submitted to the Data Coordinating Center for review by the CKD PAS Committee.
- 2) There will be a two-step review by the PAS Committee. The first step is to have the proposal reviewed for its concept and general acceptability. This will be done in 2-4 weeks after submission. A short description of the study including the following information should be submitted.
 - a) Hypotheses to be tested.
 - Specific outcome variables that will be assessed.
 - Need for data and specimens from the DCC or Repositories.
 - b) Significance of the proposed ancillary study.
 - c) How will performance of this ancillary study affect each CKD Study?
 - Specifically:
 - i. Will there be any data/specimen/image collection beyond that specified in each CKD Study protocol? If so, what additional information/samples will be obtained? What, if any, impact will this additional information/sample

- have on the main study, including study coordinator burden?
 - ii. How much additional participant burden and time will be required to complete this ancillary study?
 - iii. Will additional funds be requested for the study and what will their source be?
- 3) If this proposal is acceptable in concept to the PAS Committee, a more detailed proposal should be written and submitted for review. This proposal should include detailed information on:
- a) Hypotheses to be tested.
 - b) Background and significance of the study.
 - c) Conduct and performance of the study including specifying the study population and the data to be collected.
 - d) CKD Study staff and DCC burden. Costs for this work need to be included in the project's support.
 - e) Sample size justification.
 - f) Quality control of the data.
 - g) Data analysis methods.
- 4) The PAS Committee will review the proposal within 2-4 weeks. The decision can be for approval, modifications with further review, or disapproval.

4.6 Publication of Ancillary Study Results

The policies regarding publications and presentations of the result of ancillary studies are the same as those governing the publications and presentations of results of the main study (see Chapter 23). These policies are designed to:

- 1) Assure timely publication of the results to the appropriate professional audiences.
- 2) Avoid premature publications of results that might compromise the performance of the main study or that might compromise the ability to publish the results in high quality peer reviewed journals.
- 3) Maintain high standards of the published material.
- 4) To guard against duplicate publication of results, unless in review articles after the results have been published in a peer-reviewed article.
- 5) Assure equitable attribution of credit to all of the professionals participating in the ancillary study and the CKD Studies.

CHAPTER 6. EVENT REVIEW SYSTEM

6.1 Event Review Committee Review

The Event Review Committee (ERC) reviews serious adverse events. The Event Review Committee adjudicates whether an SAE was possibly, probably, or definitely caused by CKD procedures or by CKD random treatment group assignment. The ERC also recommends or confirms study treatment end points by which a participant continues to be followed in CKD but physicians discontinue treatments aimed toward reaching the participant's randomized treatment group assignment.

6.2 COMBINE Review of SAEs

The COMBINE Study ERC will review the first 10 SAEs occurring at each site in the COMBINE Study. After that, the ERC will review all deaths, all SAEs that the site investigators categorized as possibly related, probably related, or related and a 10% QC subset of the SAEs that the site investigator categorized as unrelated.

The following SAEs will be reported in detail to the DCC, Data Safety Monitoring Board (DSMB) and the ERC:

1. Death
2. Life-threatening event
3. Hospitalization
4. Prolongation of hospitalization
5. Congenital anomaly
6. Persistent or significant disability/incapacity
7. Important medical event requiring medical or surgical intervention to prevent serious outcome
8. Spontaneous abortion

Participants will stop treatment with nicotinamide and/or lanthanum carbonate, but data collection will continue as usual, if the site investigator and the ERC agree that an SAE was possibly, probably, or definitely related to treatment and that it is unsafe for the patient to continue on the specified treatment (nicotinamide and/or lanthanum carbonate).

The ERC will review SAEs and any events that the clinical centers categorize as requiring treatment discontinuation for safety reasons.

6.3 BASE Review of SAEs

The BASE Study ERC will review the data for any participant who is told to stop blinded medications for safety reasons. The ERC will confirm whether or not the participant met the protocol definition to stop blinded medications for safety reasons.

Emergency unblinding is not expected to be necessary as knowledge of the treatment group would not affect clinical care. The *potential* side effects of sodium bicarbonate, such as edema, hypertension, and hypokalemia are common in CKD and those taking diuretics and can be managed without unblinding the treatment assignment of the participant. In the rare circumstance that the investigator feels that unblinding would be helpful or influence participant

management, the investigator will formally request unblinding. Unblinding will be reviewed and confirmed by the ERC.

The following SAEs will be reported in detail to the DCC, Data Safety Monitoring Board (DSMB) and the ERC:

1. Death
2. Life-threatening event
3. Hospitalization
4. Persistent or significant disability/incapacity
5. Emergency room visit for:
 - a) Edema, heart failure, or pulmonary edema
 - b) Hypertension
 - c) Low serum potassium level
 - d) High serum potassium level
 - e) High serum bicarbonate level
 - f) Low serum bicarbonate level.

6.4 Event Review Committee Membership and Calls

Event Review Committee membership consists of John Middleton, M.D., from Duke University, Thomas Hostetter, M.D., from University Hospitals and Linda Fried, M.D., from the VA Pittsburgh Healthcare System. Event Review Committee conference calls will also include representatives from the DCC.

6.5 Processing documents for review

Site SAE/Death data packets are generally 5 to 10 pages long. Given that all data from the CKD database is also included in the reports sent to the Event Review Committee (ERC), it is anticipated that most SAEs would include 20 or fewer pages of additional information from the site. If a clinical center is considering sending documentation more than 30 pages in length, the site PI should carefully consider whether the physicians on the ERC need to see each page in order to understand the SAE. We are trying to keep the maximum pages for each case to 20 pages, but certainly can send more if relevant information supporting the case exceeds 20 pages.

Primary material that should be included, if available

- For hospitalizations: Discharge summary
- For ER visits: an ER summary note
- For deaths: an expiration summary, autopsy report, or death certificate

If these are not available, the CKD physician who is most familiar with the SAE should write a narrative explaining what is known about the SAE.

Supporting material that should be included, if available

- Results of laboratory tests that clarify what happened, support a primary or secondary diagnosis, or support causation. For example, if the primary diagnosis was MI and cardiac enzyme tests are available, these should be included.
- Results of procedures that clarify what happened, support a primary or secondary diagnosis, or support causation. For example, if relevant EKG tracings or biopsy reports are available, these should be included.

Be sure to list any other supporting material on Form 540 in the “Other information sent” field. If other information is sent, describe other material provided in the text box on the form. Please do not send the participant discharge instructions, as this document does not yield adequate information for the reviewing physicians.

Material that need not be included

- Do not include CKD data forms. The DCC will create a report with demographic information, labs, medications, and the contents of Form 532 (for deaths) or Forms 512 and 522 (for other SAEs and hospitalizations) that have already been entered into the CKD database.
- Discuss other documentation with the site PI or the CKD physician who is most familiar with the SAE.

6.6 How is the documentation de-identified?

DCC staff will coordinate the receipt and distribution of documents. All supporting patient documentation to be sent to the ERC should be de-identified by the clinical center staff before it is sent to the DCC. This can be done by copying the original documents and placing white out or white correction tape over patient identifiers and then using a black Sharpie marker to black areas that were covered with the white out or correction tape. This “double cover” will ensure that patient identifiers cannot be seen.

Reports that are generated are for internal CKD use and are only seen by the DCC and the ERC. Therefore, any patient information (discharge summaries, autopsies, lab tests, etc.) that is sent to the DCC will need to be de-identified. Sites should remove all types of direct identifiers that we do not store in the CKD Database. These include:

1. Names, initials (name of the participant, doctor, PI, and name of hospital)
2. Addresses
3. Phone numbers
4. [Social Security numbers](#)
5. Local medical record numbers or other local codes that directly link to an individual patient’s identification
6. [Health insurance](#) numbers or other account numbers
7. Device identifiers or serial numbers
8. Date of birth

6.7 How is the documentation sent?

Before sending material to DCC, the local clinical center personnel should write the participant study ID number and alphacode on each page of the packet being sent.

Complete Form 540 Event Information Sent to the DCC on paper prior to emailing hospitalization, ER visit or death information packets to DCC. Documentation should be scanned and sent via email to: brittak@ccf.org and sherers@ccf.org. *Please do not send to ckd_dcc@bio.ri.ccf.org.* Enter the Form 540 once the packet has been emailed successfully.

6.8 Adjudication Process

The DCC will coordinate Event Review Committee conference calls to discuss the cases. Before forwarding the information to committee members, the DCC will check that the clinical center staff appropriately de-identified the material. If necessary, they will complete the de-identification process.

The Event Review Committee will receive and review the supporting documentation surrounding the event and material from the completed SAE form and elsewhere in the CKD database to make their assessment.

A “Primary Reviewer” will be assigned to each SAE. All reviewers are sent all documentation and should review every case that will be discussed on the call. The appropriate Event Review Committee forms (Forms 612, 622 and/or 632) will be completed based on the discussions for each event reviewed.

6.9 Email Alerts

If the Event Review Committee feels that a SAE is “possibly”, “probably”, or “definitely” related to the blood pressure regimen, device, procedure or intervention that was specifically done as part of the CKD Trial Protocol, then the clinical center will receive an email alert.

All email alerts should be discussed at the next clinical staff meeting. If the center PI would like to discuss the case, the center PI should contact members of the Event Review Committee.

**Manual of Operations Chapter 6
Setting up the Clinical Sites**

Appendix 1. Early steps in setting up a Pilot Clinical Trials in CKD Clinical Center

The following local Clinical Center questions can be investigated at any time before participant enrollment begins:

- Where is the -80 freezer that the COMBINE Staff will use for FGF23 samples?
- Where will meds be shipped and to whose attention? Where will meds be stored? Who will keep track of what is received (likely by kit)? (What is dispensed will be recorded by bottle number in the study database.)
- Will a physician need to write a prescription for the study meds?
- Where will the pills be counted (out of the patient's site)?
- Is there a shelf for the patient 3-ring binders?
- Where is there a Windows desktop or laptop for data entry, or does one need to be ordered?
- How will we order the screening lab tests in such a way that they will be billed to the study and not to a participant?
- The Core Lab Spectra will supply blood draw kits and 24-hour urine jugs. Where will these be stored?
- Where will the local screening blood be drawn? Who will draw them? Is this the same person who will draw the follow up bloods?
- Where will the follow up bloods to be sent to the repository be spun? Will the same person who draws the blood be the one who spins it in a centrifuge?
- Where is the dry ice kept at this hospital? What do I need to do to get dry ice?
- Will one of our study coordinators need to be certified to do hazardous shipments or is someone else at our hospital designated to do this?
- Who do we contact to schedule the MRIs?
- How will we order the MRIs in such a way that they will be billed to the study and not to a participant?
- Who will prescribe the IV furosemide for the BOLD Renal MRIs? How will we cover lunch after morning fasting MRI, before afternoon blood draw?
- Order the cryovials you will use to ship samples from your site to the University of Washington Core Lab. You'll be shipping 2 serum and 1 plasma at B1 and F12. You'll be shipping 1 plasma at B2, F1, F2, F3, F6, F9.

CHAPTER 8: FORMS COMPLETION, DATA ENTRY AND COMPUTING

8.1 Forms Completion

The Study Coordinator will review all data forms for completeness and accuracy and to ensure timely submission to the Data Coordinating Center. Data forms will be filed in an area convenient for study personnel's access. To ensure that the study has quality data, team members must know the purpose of the study, the protocol design, and the sections of the Manual of Operations that are pertinent to their role in the study. If protocol expectations and study goals are clear and common to all team members, then protocol adherence by staff will help ensure quality data collection and a pleasant working environment.

All study forms should be completed legibly using a blue or black pen. If an error occurs when completing an entry on a form, put an "x" through the incorrect entry and write the correct entry next to it. In the margin, next to the fixed entry, write your initials and the date the change was made. Never, try to place the correct entry over the incorrect entry. Do not transcribe a form from the original completed version onto another form. However, in the rare case that a form gets something like coffee spilled on it and you are worried that you will no longer be able to read some of the values, complete another form, let the coffee spill dry out and staple the coffee stained form to the transcribed form.

Each form has a "**Clinical Center Use Only**" box which is located at the end of every form. This box should only be completed once the form is successfully data entered into the database. If you receive an error message and are unable to commit the form, do not complete any of the information in this box. Once the form is successfully saved, write the username of the person entering the data and the date the form was entered into this box. This information will also be displayed on the database screen.

All data entered into the study database should always match the paper form. Data should be entered within 3 business days from the date the visit was held.

8.1.1 Screening Forms and dropout

If the Screening Form shows that the participant is not eligible for the study, a dropout form is not needed.

8.1.2 De-Identifying the Participant Consent and Forwarding to the DCC

In order for a participant to be randomized, the DCC will need to receive a de-identified copy of the signature page only of the consent form for the participant to be randomized. We do not need the entire consent; only the signature page. Please make sure that all participant information cannot be seen by DCC staff. This can be best done by using a black marker. The DCC should be able to see the date the participant signed the consent though.

Write the Participant ID and Alphacode in the middle of the page. This way, if it is faxed to the DCC, we will be able to see it and this information will not be cut off.

It is best if this document is scanned and emailed to ckd_dcc. However, if you do need to fax it, please send an email to ckd_dcc stating that you are doing this.

8.2 CKD Study Computing

The CKD Study Data Coordinating Center's recommended specifications for your PC are as follows:

Internet Explorer 6.0 or higher, Adobe Acrobat Reader, and the Sun JRE download for the Oracle 11g application. These can be downloaded from the DCC's website as specified in Appendix A.

8.3 Accessing the DCC Website to Enter Data

See Appendix A for instructions on how to set up your PC to access the DCC's website.

After you have successfully entered the website, you will see a menu titled 'CKD Study'. At this point, resize the window to the largest that will fit on the screen for optimal viewing. You can then choose a form or report from the menu, or you can go to the 'Inquiry' menu to answer or view your data inquiries.

8.4 Usernames and Passwords

You will have an Oracle database username and password. The usernames are assigned by the DCC's Database Administrators and are usually set up in the following format: first six letters of your last name followed by the first letter of your first name. There are up to seven letters in a username. Please do not share passwords. Passwords are not case sensitive.

Passwords will need to be changed every 75 days. You will be notified via email when your oracle password needs to be changed. If you do not change your password in the allotted time, you will need to send an email message to CKD_DCC@bio.ri.ccf.org asking to have your password reset. A new temporary password will be sent to you in a secure e-mail and you will need to retrieve it from the secure site. This temporary password is only valid for one day..

8.4.1 Selecting a Good Password

Here are some good references for picking a good password:

- http://www.net.berkeley.edu/dcns/faq/good_pw.html
- <http://www.msc.tamu.edu/services/cops/security/goodpasswd.html> and
- <http://www.cs.umd.edu/faq/Passwords.shtml>

Please read them all as they all have good advice.

8.4.2 Changing Your Password

There is a menu option available to change your password.

1. Go into the CKD Study website <https://qhsapps.ccf.org/ckdp/> and click on 'Logon to the CKD System'
2. Enter your username and current password then hit 'enter' or click on 'connect'.
3. At the top of the screen, click on 'Change your password' and follow the prompts. Be sure to select 'RDP10' as the database. Passwords for the CKD Study will require 8 or more alphanumeric characters (alphanumeric characters include letters and numbers only). An alpha character must always appear in the first position of the password.

8.5 Instructions: How to Enter Study Data into the Database

Press enter, tab or click your mouse to move from field to field within a form. Note that you will see bubble help when you move your mouse over the toolbar buttons. The upper left button should be the 'Save' button. When you are finished entering data for a form, click on the save button, or choose 'Save' from the 'Action' menu, or press the Ctrl+K to identify which key is the 'Save' or 'Commit' function key. The Ctrl+S key corresponds to the Oracle function 'Save' or 'Commit'.

Maximize window to see messages at the bottom of the screen. You will see a message indicating how many new records were added to the database. You can get out of a form by pressing the 'Exit' button or choosing 'Exit' from the 'Action' menu. 'F4' is the speed key to exit.

If you want to enter another form you should navigate to the top of the form, and press the 'Insert Record' button. 'Insert' can be selected from the 'Record' menu. Unfortunately, you are not permitted to remove records once you have saved/committed them. You will need to send the DCC a data change request via the Inquiry system to do that. You are also not permitted to change certain key fields or fields that determine eligibility. Again, you will need to send a query to the DCC.

When entering data, if you receive an error message stating the value is out-of-range, then back out of the form without saving the information and review the data with other staff members and possibly the PI. If the value on the paper form is correct, notify the DCC with the information and we can investigate further. It may be that the range needs to be adjusted for that particular field. **Never** enter a value as a placeholder thinking that you will come back and fix the data at a later date.

If a form requires that all fields have a response but your paper version of the form has fields that are blank, **never** enter a value as a placeholder thinking that you will come back and fix the data at a later date. Instead, back out of the form without saving it. Discuss the form with other study personnel and the PI to obtain values for those fields that were missing.

8.5.1 Obtaining the ID and Alphacode for a Participant

When data entering the Screening Form for each study, question 1 “Identification Number” will have a list of values key (^), click on the “^”. Select the first identification number that is listed. Once you have selected that number, that number will not be displayed the next time a Screening Form is entered. The Alphacode will be populated once you have successfully committed and saved the Screening Form. Make sure to write the Identification Number and the Alphacode on the Screening Form. This ID and alphacode will follow the participant throughout the study.

8.5.2 Keymappings

Ctrl+K means hold down the <Ctrl> key and then simultaneously press the ‘K’ key. Now release ‘K’ and then <Ctrl>. Another way to get to the key mappings is to choose ‘Keys’ from the ‘Help’ menu.

8.5.3 List of Values (LOV)

Note that you may see messages on the bottom of your screen. If you see ‘List of Values’, that means you can choose ‘Display List’ from the ‘Edit’ menu, or press Ctrl+L to retrieve a list of values to your screen which you can scroll through and make a selection. You can also click on the ‘v’ button next to the field to select the response you need.

8.5.4 Editing

If the box for the field is smaller than the text you are typing into it, you can choose ‘Edit’ from the ‘Edit’ menu, or press Ctrl+E when your cursor is in that field. This will open up a pop-up box containing a larger view of that field.

8.5.5 Navigation

Other useful Oracle functions that you can use are ‘Next Record’ and ‘Previous Record’. You can find buttons and speed keys for these and they are also on the ‘Record’ menu. Use these to navigate between forms or detail records (for example, in the medication form).

8.5.6 Error Messages

If you skip over a required field, you will see the error message:

Field must be entered.

If you enter a value that is not possible for that field, you will see the error message:

Invalid value for field name.

If you enter a non-numeric character in a numeric field, you will see the error message:

Legal characters are 0-9 - + E or Item must be formatted as, for example, 90.0 (or some specific format)

If you try to update previously entered data without using the [Change Value] button, you will see:

Field is protected against update.

If you try to enter a Form that has already been entered, you will see the error message:

Error while inserting: ORA-00001: unique constraint (P200723.BID_CC_PK) violated.

You will also see other various error messages as well. If you can't figure out why you are getting that particular error message, please write down the complete message, and also choose Help->Display Error while the message is on the screen to see if a further explanation pops up before contacting the DCC. If you get stuck, it may help to use Cancel Query or Query->Cancel (if you see 'Enter-Query' on the bottom of your screen), Action->Clear All or Record->Clear

8.6 Instructions: How to Change Study Data in the Database

8.6.1 Retrieving Data

Once the data has been entered, you can retrieve it to your screen for viewing:

- Access the form # you want to view.
- Press the F11 [Enter Query] key, query icon or use the pull down menu option under 'Query'.

Note the hint line will say 'Enter-Query'.

- Enter the Patient ID, Visit Type and Visit Number (visit number may not be applicable).
- Press the Ctrl+F11 [Execute Query] key, execute query icon or use click on the pull down menu option under 'Query' to execute query.

8.6.2 Data Change Within 7 Days

- Retrieve the form you want to view.
- Put the cursor on the field that needs to be updated.
- Press the [Change Value] button.
- Change the value by entering the appropriate value.
- Press 'enter' or [Save] button.
- A pop-up box will appear with a Data Change Number.
- Write the Data Change Number on your form next to the question that was changed.

- Press the [OK] button to return to the form.
- No further action is required.
- The database should always match the paper copy of the form you entered.

8.6.3 Clinical Center Change to Data After 7 Days (send ‘Data Change Request’ to DCC)

- Retrieve the verified data and the form you want to view.
- Position the cursor on the field to be changed.
- Press the [Change Value] button.
- A new screen will appear that will allow you to enter a ‘New Value’ and an explanation.
- Enter the new value in the ‘New Value’ field and text describing the desired change in the ‘CC Text’ field. Please give as much detailed information as possible as to why the value should be updated. (The DCC will use this response to investigate the request.)
- Press the [Save and Exit] button.
- You will receive an inquiry number or ‘data change request’ number after you save the request. Write this number on your form. You can use this number to check to see if the DCC signed off on your inquiry.
- The DCC will take the appropriate action, and then use the DCC Sign-Off screen to indicate the final status of the request.
- A ‘DCC Sign-Off to CC Initiated Data Inquiry’ will be sent to the DCC and CC.
- No further action is required.
- The database should always match the paper copy of the form you entered.

8.6.4 Data Change for Forms 9 and 10

- Data on Forms 9 and 10 can be changed at any time.
- Retrieve the data and the form you wish to view.
- Put the cursor on the field that needs to be updated.
- Change the value by entering the appropriate value
- Press the [Save] button.
- No further action is required.

8.7 Instructions: How to Initiate and Respond to Data Change Requests/Queries

8.7.1 Clinical Center Initiation of Queries

Queries, or Data Change Requests, can be initiated by the Clinical Center as described in the above section on changing data.

8.7.2 Clinical Center Response to a DCC Initiated Inquiry

- You will receive a DCC initiated inquiry report through e-mail, or you can go to the 'Inquiries' menu and choose 'Center Response to DCC Inquiry' to find unanswered queries.
- To respond to an inquiry, you **must** use the database Inquiry System. The DCC is unable to accept e-mail responses.
- When the screen appears you can press [Execute Query] to retrieve all unanswered queries, or press [Enter Query] and enter the specific query # and then press [Execute Query].
- If you do not enter an inquiry number, all unanswered queries will be retrieved. You need to press [Next Record] or use the 'up' or 'down' arrow' key to navigate to the other queries. Keep pressing [Previous Record] to get back to a previous query.
- Position your cursor on the 'DCC text' field'.
- Choose Edit->Edit if you want to read the entire explanation from the DCC as to why you are being queried.
- Navigate to 'New Value'.
- Type a new value for the field being inquired. If a different field requires changing, leave it blank or enter N/A for not applicable.
- Navigate to 'CC text', and enter an explanation for your value. This field must be answered in order for the DCC to take action. Please make sure that your explanation is specific and complete.
- The explanation can be up to 2000 characters. Click on the [Save and Exit] button on the bottom of the screen to save the text. Click on [Exit and Don't Save] if you do NOT want to save the text.
- The DCC will then make the appropriate updates to the database.
- It is very important that the CC respond within 3 business days.

8.8 Retrieving Data from Forms

8.8.1 Introduction

Data can be retrieved in several ways from the form application. In order to ‘query’ data available in the database for the information on a given form application, the [Enter Query] and [Execute Query] keys can be used. The screen will be populated with the first set of patient data for the form application being accessed. By pressing the [next record] or [previous record] keys, you will have the ability to view the next or previous set of data.

There are different ways to retrieve data. You can execute simple queries that meet specific criteria, as well as complex queries that satisfy several conditions. The following topics are discussed.

- Matching exact values
- Entering variable conditions
- Matching values that meet a specified pattern

8.8.2 Matching Exact Values

Suppose you want to check on all instances of visits of the 'B' or 'F' type for a given patient ID (110001 for example). The data entry screens can retrieve the record(s) that contains specifically these values. The following are general steps for retrieving records that match exact values:

1. Access the appropriate form via the menu system.
2. Press [Enter Query]
3. Type the values you want to match into the appropriate fields.
4. For this example, cursor to the Patient ID field and type 110001.
5. Press [Execute Query]
6. Press [Next Record] or [Previous Record] to view the retrieved data.

NOTE: If there is not any data that meets the specified criteria, the following message will be displayed on the status line of your screen:

‘FRM-40301: Query caused no records to be retrieved. Re-enter.’

8.8.3 Entering Variable Conditions

Sometimes it is not practical to enter the exact values that you want retrieved data to match. For example, you might want to retrieve the following:

- A specific form with visit type = ‘F’

To select data that have a visit type = 'F', press [Enter Query] and enter the patient ID number, visit type of 'F' and press [Execute Query]. This will bring up all of the forms with a visit type of 'F' for that participant.

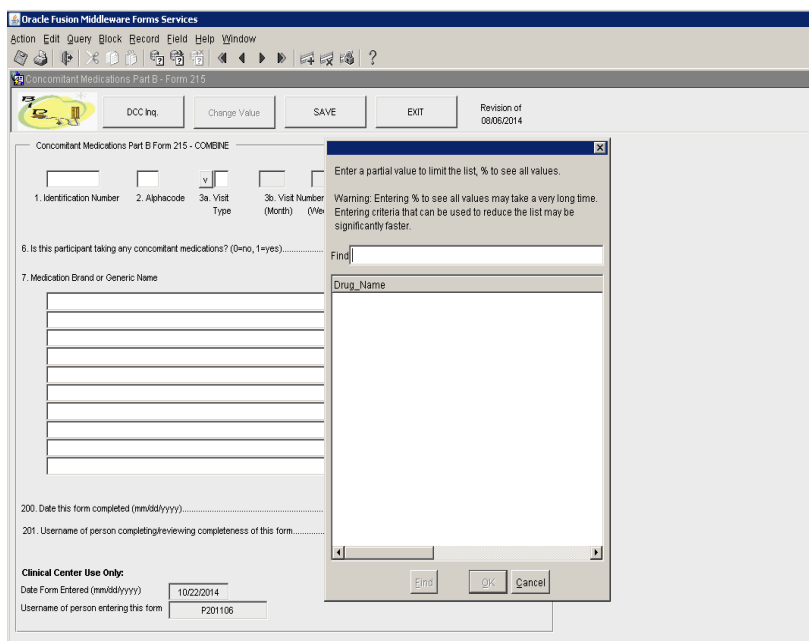
8.8.4 Populating WHOdrug and MedDRA Data Fields

A. The WHO Drug database is used for recording medications on Form 214-Concomitant Medications, Part A and Form 215-Concomitant Medications, Part B. You will need to select the name of the medication from a [List of Values] to populate these forms; you cannot type freehand the name of the medication as there is a chance of misspelling.

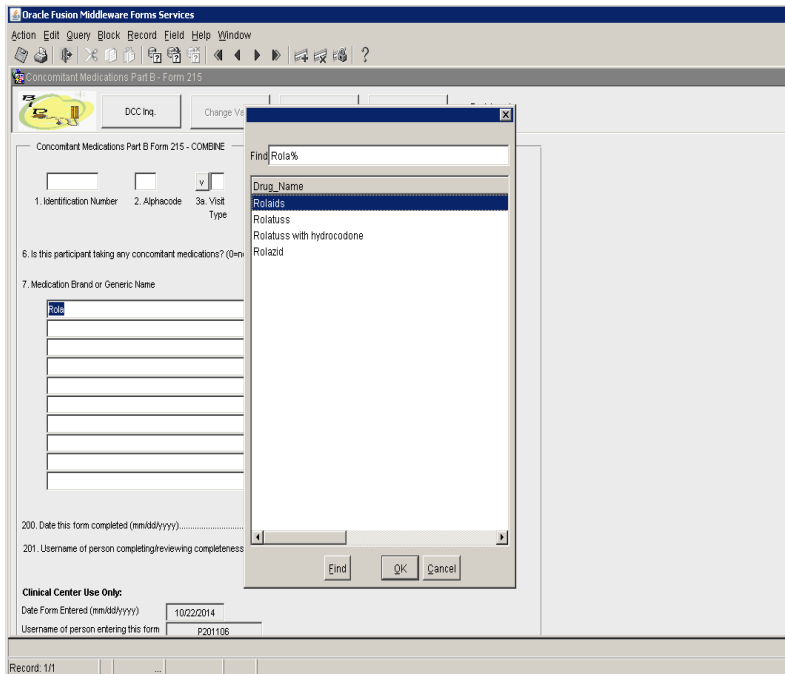
For example, a patient is taking a non-antihypertensive medication, Rolaid's, on Form 215:

1. Access the Form 215 data entry screen and enter the patient information in Q1 - 6.
2. Database will automatically pop you into a blank medication field.
3. Obtain the medication name by clicking on the [List of Values] box on the left side of the field and you should get an empty pop-up box.

(pop-up box shown on next page)



4. In the 'Find' box, type the first few letters of the medication name 'Rolai' (not case sensitive) and the window will automatically add the % sign. Either hit the 'Enter' key or click on the 'Find' button at the bottom of the window. The window will populate with all medications starting with those 5 letters.



5. Scroll through the list of medications to identify the name of the medication the patient is taking. (*Disregard the country and drug code number.*)
6. You can further refine this same list of 413 medications by going to the 'Find' line and typing in the additional letters and the window will provide a smaller subset of medications.
7. Using your mouse, highlight the medication name and click the 'OK' button. The blank medication field will now be populated with the medication name. Another option is to highlight the medication and double-click. The field will be populated.
8. **Note:** if you determine that the name of the medication is different than what you originally typed, you must click on the 'Cancel' button or the 'X' box and start over.
9. If there are no other medications to be entered, you can either press the "enter" key twice to go to the next question or use your mouse to go to the next question. However, if you press "enter" and type something in the blank row and delete it, you will not be able to exit that row since the computer is expecting you to enter another medication. If there are no other medications to be entered, and the cursor will not go to the next field, select "Record" from the task bar, then select "Remove". You will then be able to use your mouse to get to the next question on the form.

B. The Medical Dictionary for Regulatory Activities (MedDRA) is a clinically validated international medical terminology. The CKD Study uses this software for miscellaneous signs and symptoms that patients may report that are not already listed in previous questions.

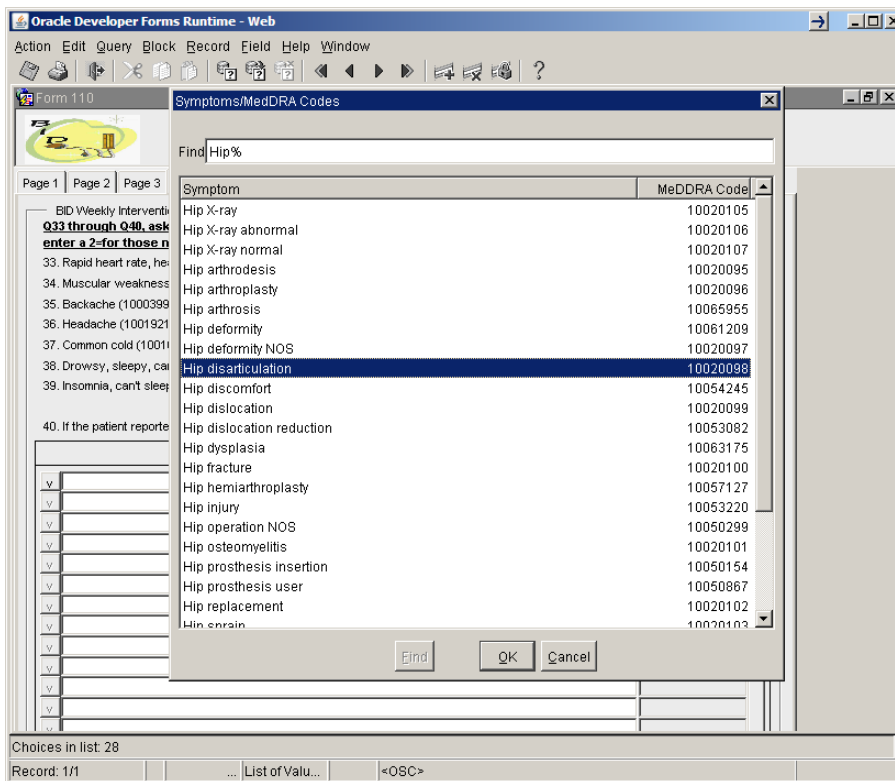
For example, a patient tells you he had 'hip pain':

1. Access the Form 285 data entry screen and enter the patient information up until you reach Q36.
2. Database will automatically pop you into a blank 'Symptom' field in Q37.

To pop out of blank Symptom field, simply hit 'Tab' or 'Enter' button. Database will automatically place your cursor in Q37.

3. Obtain the symptom name by clicking on the [List of Values] box on the left side of the field and you should get an empty pop-up box. (*The pop-up box is the same as the picture shown in the medication section 8.7.4. above.*)
4. MedDRA advises that in searching for symptoms, use what the patient reports. Do not attempt to interpret what the patient reports.
5. In the 'Find' box, type the first few letters of the symptom 'hip' (not case sensitive) and the window will automatically add the % sign. Either hit the 'Enter' key or click on the 'Find' button at the bottom of the window. The window will populate with all symptoms starting with those 3 letters.

(pop-up box shown on next page)

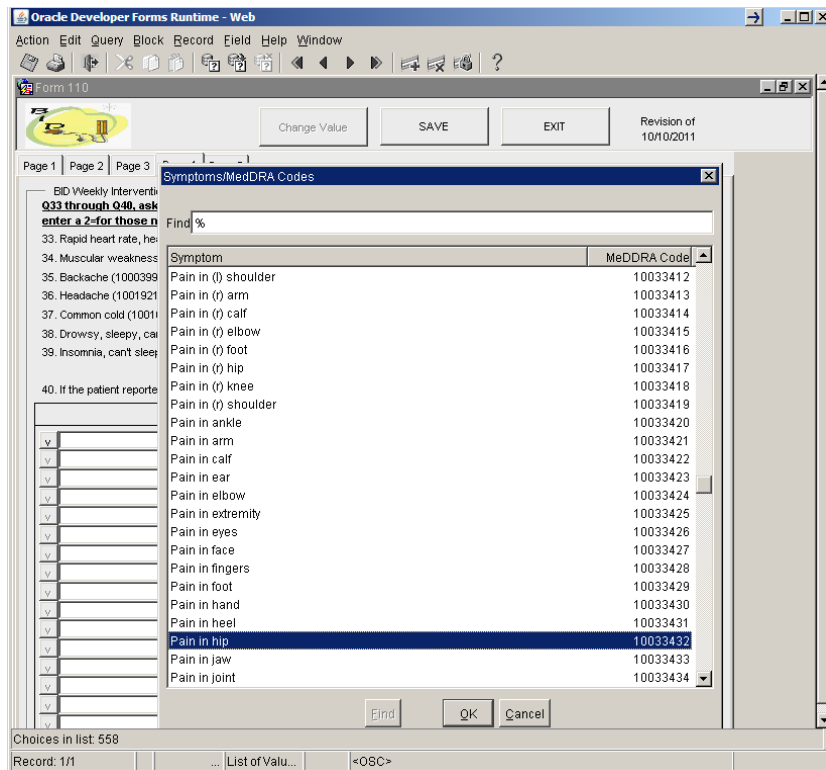


6. Scroll through the list of hip-related symptoms to identify what the patient reported. (Disregard the country and drug_code number.)

- You can further refine this same list of 28 hip-related symptoms by going to the ‘Find’ line and typing in additional letters; the window will provide a smaller subset of symptoms.

In this example, there is no ‘hip pain’ listed. Cancel out and start over by typing a slight variation of ‘Pain in hip’ typed as ‘pain’ %. This brings up 558 symptoms with ‘pain’ as part of the description. As you can see in the pop-up box shown on the next page, two symptoms ‘Pain in (l) hip’, ‘Pain in (r) hip’ or ‘Pain in hip’ are identified.

(pop-up box shown on next page)



Select the symptom that best represents ‘hip pain’ reported by the patient.

- Using your mouse, highlight the symptom name and click the ‘OK’ button. The blank symptom field will now be populated with the symptom description. Another option is to highlight the symptom and double-click; the field will be populated.
- Note:** if you determine that the symptom is different than what you originally typed, you must click on the ‘Cancel’ button or ‘X’ box and start over.
- If there are no other symptoms to be entered, you can either press the “enter” key twice to go to the next question or use your mouse to go to the next question. However, if you press “enter” and type something in the blank row and delete it, you will not be able to exit that row since the computer is expecting you to enter another symptom. If there are no other

symptoms to be entered, and the cursor will not go to the next field, select “Record” from the task bar, then select “Remove”. You will then be able to use your mouse to get to the next question on the form.

8.9 Patient Confidentiality and Data Security

Patient confidentiality of medical records and identity will be maintained at the highest level. All patient data submitted to the DCC will be transmitted as secured encrypted files and reported anonymously with no names, Social Security numbers, etc. It will be emphasized to all staff of the CCs, and any central cores, the need for strict confidentiality of all study data, with a specific plan for later data sharing as required by NIH. HIPAA privacy regulations will be followed carefully. All forms, CDs and tapes will be kept in locked cabinets. All computerized files will be protected by means of a password system. All reports prepared by the Data Coordinating Center will be such that no individual patient can be identified. Any publication of trial data will be reported as a group, thus avoiding identification of an individual subject.

8.9.1 System Physical Security

The Server Room is located on the Cleveland Clinic main campus in the JJNorth Building. Building and department access is limited to authorized Cleveland Clinic and contracted maintenance employees via ID Badge swipe access device at building entrances. The Server room access is restricted to authorized personnel only via ID Badge swipe access device at the server room entrance.

Devices and systems for fire detection are installed and available. Server room undergoes periodic fire marshal inspection by the Department of Safety.

Temperature and humidity are automatically controlled by the heating and air conditioning equipment. Server and battery room temperatures are monitored automatically. Facility Engineering is notified of high temperature alerts for remediation automatically. The System Group is notified at the same time.

A UPS (uninterruptible power supply) is installed, maintained and tested periodically to allow for proper computer equipment shutdown in the case of extended power outages. The UPS automatically sends a page if it goes on.

8.9.2 Storage and Back-up

The database is backed up weekly in its entirety using Oracle Recovery Manager hot back-ups. Then incremental ‘hot’ back-ups are done on a daily basis. These are all written to disk where they are in turn copied to tape backup. In addition, transactions between backups are stored in archive logs that are also on hard disk. The tapes are kept in a fireproof safe on site for one month and then moved to Iron Mountain for long-term storage.

8.9.3 Auditing

CKD Study data are contained within an Oracle database. Access is through password protected user accounts. Passwords are forced to be changed at least every 75 days.

All inserted data records are stamped with the date, time and username of the person entering the information.

All changes to data records have a copy of the existing record saved in an audit table and the date, time and username of the person making the change is saved.

All data record deletions have the existing record copied into an audit table along with the date, time and username of the person deleting the record.

8.10 E-mail Alias Lists

There are several useful e-mail aliases, including:

ckd_steering@bio.ri.ccf.org -	Steering Committee
ckd_dcc@bio.ri.ccf.org -	DCC personnel
ckd_exec@bio.ri.ccf.org -	Executive Committee
ckd_forms@bio.ri.ccf.org -	Forms Committee

Other alias listings can be found in the CKD Study Address Directory.

Appendix A

CKD Study Website

WEB SITE DOWNLOADABLE UTILITIES

The upgrade/install to our Oracle Forms application for the CKD Study is to allow sites to use Java 8. Please follow the steps below to update your Java. Please note that if you don't have permission, you may need to contact your local IT support.

A. Go to:

<http://www.java.com/en/>

1. Click on the link "Do I have Java?" to obtain your current version.
2. Click on "Verify Java version"
3. Click on "Download Java Now" to get Version 8 Update 111 32 bit
4. Click "Agree and Start Free Download"
5. If you get a pop-up box at the bottom of your screen that says "Do you want to run or save JavaSetup8.....exe (721 KB) from sdlc-esd.oracle.com?", then click "Run"
6. On the "Welcome to Java" page click "install"
7. Uncheck the box "RECOMMENDED....." by checking 'Do Not Update Browser Settings' and click "Next"
8. Java will install
9. If 'Out-of-Date Java Version Detected' – press 'Uninstall' (older version)
10. If you see: "Restore Java security prompts" Uncheck and click "Next"
11. Once finished, close all browsers and restart

You have successfully installed Java and may or may not need to do the following steps below in 'B':

B. Please leave the check mark in "Restart my browser now to complete the installation" and click "Close"

1. Java will close and re-open in another window. Click "Enable" where it says "The Java™ Plug-In SSV Helper add-on from 'Oracle American, Inc.' is ready for use"

C. Go to the computer Start button, left click and select the Control Panel.

1. Select Java and click on the "Security" tab.
2. Click on "Edit Site List"
3. Click "Add" and type the following into the box labeled 'location': <https://qhsapps.ccf.org> and press "OK".
4. Close your browser and restart to access the CKD Database.

Appendix B

Key Mapping

FUNCTION	KEY
Block Menu	Ctrl+B
Clear Block	F7
Clear Field	F5
Clear Form	F8
Clear Record	F6
Commit	Ctrl+S
Count Query	F12
Delete Record	Ctrl+↑
Display Error	Shift+Ctrl+E
Down	↓
Duplicate Item	Shift+F5
Duplicate Field	Shift+F6
Edit	Ctrl+E
Enter Query	F11
Execute Query	Ctrl+F11
Exit	Action menu, select Exit
Help	Ctrl+H
Insert Record	Ctrl+↓
List of Values	Ctrl+L
List Tab Pages	F2
Next Block	Shift+PageDown
Next Field	Tab
Next Primary Key	Shift+F7
Next Set of Records	Shift+F8
Previous Block	Shift+PageUp
Previous Field	Shift+Tab
Print	Ctrl+P
Return	Return
Show Keys	Ctrl+K
Up	Up
Update Record	Ctrl+U

Appendix C

Instructions on Running the “Bottle Number Assignment Report”

Login to the CKD database

Under “Forms”, click on “Assign Bottles-COMBINE”

Enter ID and Alphacode for the participant

After entering the participant ID and Alphacode, your site will receive a message that the query produced no records. (That is fine because this is the participant’s first bottle assignment.)

Place a “B” in the “Visit Type” field and a “0” in the “Visit #” field for the Baseline Visit. For follow-up visits, place a “F” in the “Visit #” field.

Press the ***Assign Bottle(s)*** button and the bottle assignment should populate under “Bottles Assigned But Not Dispensed”.

Your site will receive an email with this same information which you may use to pull the bottles for participant.

Note: This report can be run the day before the participant receives the baseline study medications. This allows time for your research pharmacy to gather the medications and will not hold up the participant visit.

Appendix D

Instructions for Clearing your IE Cache

If you are unable to see an updated report, try cleaning out your 'cache' in your web browser and then try running the report again.

You can follow these steps:

- a. Open Internet Explorer and then click on Tools.
- b. Then click on Internet options.
- c. Click the General tab, and then, under Browsing history, click Delete.
- d. Here you can select history, cookies, temporary internet files and then click delete.

This will clear your Internet Explorer cache.

Chapter 9, Appendix 1: CKD Study eGFR Equation

CKD-EPI equation expressed as a single equation:

$$\mathbf{GFR = 141 \times \min (Scr / \kappa, 1)^\alpha \times \max(Scr / \kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}}$$

where:

Scr is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of Scr / κ or 1, and

max indicates the maximum of Scr / κ or 1.

Chapter 9, Appendix 2: BSA Formula

The DuBois formula is used to calculate BSA.

$$BSA = 0.007184 \times W^{0.425} \times H^{0.725}$$

CHAPTER 11. GENERAL PRINCIPLES OF RECRUITMENT FOR THE U01 CKD STUDIES

11.1 General Issues of Recruitment

Recruitment is essential for the success of this study. Consider the following points when recruiting participants:

1. Emphasize the importance of the study.
2. Emphasize the nutritional information that will be provided during the study.
3. Emphasize close follow-up of laboratory results during the study.
4. Explain that a stipend for participation will be provided.
5. Approach potential participants more than once, if necessary.
6. Be courteous, attentive and professional.
7. Show interest and enthusiasm in the study.
8. Make sure that potential participants fully understand the potential risks and benefits of the study. Explain all aspects of the study detailed in the informed consent. Make sure that participants understand the information you present. Allow the participant enough time to consider and sign the informed consent document.
9. Emphasize that participation in the study will advance medical knowledge. Potential participants may be told, “We don’t know the answers, but here is a chance to help medical science.”
10. Some potential participants will be motivated by stressing that the results may benefit future generations of patients with chronic kidney disease and that they may have a chance to help society.

11.2 General Issues Regarding Contact with Providers and Participants

Several tools are available for establishing contact with providers and participants.

11.2.1 Provider Cooperation

Providers are busy, and it is not their responsibility to recruit participants for this study. But you can ask for their support.

1. Take the initiative. Do not wait for providers to contact you regarding potential participants.
2. Mail a study brochure with a personal letter to providers requesting their cooperation.
3. Ask providers for permission to contact their patients and ask them to encourage their patients to enroll.
4. Reassure providers that their patients will be followed by individual CKD study (COMBINE, BASE, Microbiome) investigators for study purposes only.
5. Let the providers know that you will inform them of the participant’s course in the study.

11.2.2 Contact with Providers

Direct involvement of investigators is essential for successful recruitment. Possible strategies include:

- **Formal and informal presentations** (Grand rounds, research conferences, house staff rounds, clinic in-services)
- **Distribution of brochures** in clinics
- **Direct conversations** with physicians and other providers (physician assistants, nurse practitioners, nurses)
- **Consistent and frequent screening** in CKD and other clinics
- **Data base searches and mass mailings**

To promote collaboration, investigators should reassure the providers that their patients will be followed by their individual CKD study (COMBINE, BASE, Microbiome) investigators for study purposes only and that providers will be informed of the patients' status throughout the study.

11.2.3 The Participant Brochure

The recruitment brochure describes in easy-to-understand language the purpose of an individual CKD study (COMBINE, BASE, Microbiome) and what is expected of the participants. It can be used as a tool to briefly review the study requirements with potential participants upon initial introduction, prior to the screening visit and the actual informed consent process. Sample participant brochure will be provided in Appendix and on the study website. This brochure requires approval by your local Institutional Review Board before it should be distributed to potential participants or providers.

11.2.4 Letters to Patients and Providers

Sample letters will be provided in Appendix and on the study website. These letters require approval by your local Institutional Review Board before it should be distributed to potential participants or providers.

11.3 Approach to Recruitment

11.3.1 Recruitment Plan

Each site will develop a recruitment plan that may use some or all of the following recruitment strategies: clinic-based recruitment; referrals from providers; community-based recruitment campaigns.

Clinic-based recruitment:

- After HIPAA waivers and waivers of Informed Consent are obtained, if required by local Institutional Review Boards, electronic medical records will be reviewed to identify potential patients who are eligible for participation.
- Study staff will approach patients during their clinic sessions and invite them to learn more about the study. Recruitment letters may also be used instead of verbal contact during the course of providing medical care. Following introduction, study staff will communicate with interested individuals and set up a screening visit.

Referral from providers:

Providers will be introduced to the study and will be provided with list of inclusion and exclusion criteria. The primary providers will be encouraged to discuss the study with potentially eligible participants, and to either provide the participant with contact information for the study, or alternative ask if study personnel may contact the participant to discuss the study in more detail. Study staff will initiate contact with interested and potentially eligible patients and

describe the study to them. Recruitment letters may also be used instead of phone contact. Following introduction, study staff will set up screening visits with interested individuals.

Community-based recruitment:

The site investigators will initiate contact with community leaders and introduce them to the study. Community leaders will suggest possible ways to disseminate information regarding the study to potential participants in the community. Study staff will respond to contact initiated by interested individuals and briefly describe the study to them. Following introduction, study staff will communicate with interested individuals and set up a screening visit. Additional strategies, including targeted mailings, advertisements within healthcare settings and external promotions will also be considered.

Additional strategies may include:

- provider referrals
- participants referrals
- targeted mailings
- advertisements within local health care settings
- external promotion

11.3.2 Monitoring Recruitment Progress

Investigators and study staff will meet weekly to discuss progress of weekly goals. Appropriate actions may include:

- Increase number of chart reviews
- Increase time in targeted clinics
- Determine what is working and what is not
- Review barriers and problems
- Revise the plan as necessary
- Consider other means of recruitment, including outside promotion

CKD Study Participant Information

These informational items are for local center adaptation only. Note: information on this sheet should be reviewed with the patient beginning at baseline and, if randomized, at F3, F6, F9 and F12.

CKD Identification Number

CKD Alphacode

Participant's Name (Last, First, Middle/Maiden)

Participant title preference (Mr., Mrs., Ms, no preference)

Social Security Number

Age, Birth date

Preferred Method of Contact/Best Time(s)

Check if Medical Records Release Form is signed

MRN (local dialysis unit, other medical establishment)

Contact Information

Pt complete addresses (home and alternate)

Pt telephone numbers (home, work, cell, alternate, fax #s)

(pt communicate by telephone? TTY phone may be an option)

Pt email addresses: (home, work, alternate)

Spouse or Significant Other: (Last, First, Middle/Maiden), title preference

Telephone numbers: (home, work, cell, alternate, fax #s)

Additional Notes

Alternate Contact(s) not living with participant (Last, First, Middle/Maiden, title preference, relationship to pt)

Telephone numbers (home, work, cell, alternate, fax #s)

Emergency Contact (Last, First, Middle/Maiden, title preference, relationship to pt)

Telephone numbers (home, alternate numbers)

Health Care Information:

Primary Care/Referring Physician Name

Address (Street, Bldg/Floor/Suite, Box/Dept, City, State, Zip)

Telephone numbers (office, fax #s)

Notes

Nephrologist or Other Physician Name

Address (Street, Bldg/Floor/Suite, Box/Dept, City, State, Zip)

Telephone numbers (office, fax #s)

Notes

Type of Insurance

Notes

CHAPTER 50. COMBINE STUDY OVERVIEW AND GENERAL INFORMATION

50.1 Blood Pressure

Although there is no central blood pressure training, staff who have been trained in blood pressure measurement can measure blood pressure in COMBINE participants.

The CKD Optimal Management with Binders and Nicotinamide (COMBINE) Trial

Appendix 1:

Items to have on hand for when the COMBINE Study starts

- Sphygmomanometer (to measure blood pressure, pulse)
- Stadiometer (to measure height)
- Weight scale to measure urine weight
 - Two COMBINE standard table top weight scales (one to use to measure urine weight; one on hand, stored, as a back-up). The standard scale chosen for COMBINE is the KD8000 Scale by My Weight - Baker's Math Kitchen Scale. (Available on Amazon.com for \$32.32)
- 500 g calibration weight
 - Need not be standardized. However, if you need to order one, you might consider the one offered by American Weigh Scales 500WGT 500 Gram Calibration Weight for \$7.65 on Amazon.com
- 200 g calibration weight
 - Need not be standardized. However, if you need to order one, you might consider the one offered by American Weigh Scales 200WGT Carbon Steel 200gm Calibration Weight Scale for \$7.21 on Amazon.com
- Male urinals and female toilet hats (to make it easier for patients to do their 24-hour urine collection)
- Pill counting tray that can handle ¾” pills and a pill-counting spatula
- Centrifuge – Capable of spinning at 3000 rpm for 15 minutes
- Freezer (-80 to -70°C) to store FGF23/R01 specimens
- Blood drawing supplies:
 - Tourniquets
 - Butterflies/needles (21G and 23G)
 - Vacutainer (needle holders)
 - Gauze
 - Coban/tape
 - Alcohol wipes
 - Pipettes
 - Local lab requisition form or method to order local labs
 - Biohazard bags or container for transport
 - Blood tubes for local labs
 - Sharps containers
 - Specimen racks/boxes for temporary storage of samples shipped monthly
 - Permanent fine-tip marker (Sharpie)

Other start up items to consider:

- A Windows desktop or laptop available for data entry
- Convenient printer
- Three-ring binders for completed data collection forms and other source documents
- Folders for giving hand-outs to study participants
- Shipping supplies, e.g., packaging tape and a box cutter
- Storage for:
 - Lab supplies
 - Study meds if you are storing the blinded meds with the PI, not the pharmacy
 - Participant study binders (follow guidelines for storing in locked cabinet, room, etc.)
- IATA certification – Necessary for any study staff member that is packaging samples for shipment
- CLIA Certificate of Waiver – If study personnel will be performing the urine pregnancy test, the site needs to check if they are covered by an institutional CLIA. If not, a CLIA Certificate of Waiver is necessary.

**Primary Reasons Why Candidates Who Were Approached
for COMBINE Did Not Consent**

	Reasons Approached Candidates Did Not Consent	Number of Patients
A.	Do not want to be in a research study / “feels like a human guinea pig” / Feels he does not need research done on his kidneys	
B.	Particularly does not want to take nicotinamide	
C.	Particularly does not want to take lanthanum	
D.	Particularly does not want to be randomized to treatment	
E.	Not willing to take a placebo	
F.	Prefers to eat fewer than 2 meals per day	
G.	Says COMBINE Pills are too big to swallow	
H.	Doesn’t want to take so many pills or so many additional pills	
I.	Too busy / Busy schedule / Doesn’t want to attend so many visits	
J.	Doesn’t want to collect the 24-hour urines	
K.	Says study is too long / doesn’t want to stay a full year	
L.	Not willing to do some other COMBINE requirement [please keep a list] <i>(Remember that you do not need to consent to the biosample repository or to MRI in order to join COMBINE)</i>	
M.	Patient does not want to participate for some other specific reason [keep a list]	
N.	Says that overall, the study requirements are just too much for him/her	
O.	Significant others do not support patient participating	
P.	Primary care doc, other nephrologist does not support patient participating	
Q.	Not ready at this time / Thinking about it / Will approach later	
R.	Other Reason [please keep a list]	
S.	Patient said no (or refused to respond despite prompting) without giving a reason	
1.	In another interventional study	
2.	Participant lives too far away	
3.	Participant does not live here all year around	
4.	Participant does not speak English	
5.	Institutionalized (nursing home or rehab center)	
	TOTAL NUMBER OF CANDIDATES THAT DID NOT CONSENT	

Appendix 3. Reasons Some Candidates Were Not Approached

	Reasons Candidates with (age and most recent serum creatinine and most recent serum phosphorus in range maybe?) were not approached to ask for COMBINE Consent	Number of Patients with this as the primary reason
1)	GFR likely too high	
2)	GFR likely too low	
3)	Likely to require dialysis soon	
4)	Likely to receive transplant soon	
5)	Known to be substance abuser	
6)	Known to be non-compliant to medications	
7)	Known to miss many visits	
8)	Seems to have very frequent hospitalizations	
9)	Seems to have too many comorbidities	
10)	Thought to have a short life expectancy	
11)	Blind	
12)	Cognitive impairment	
13)	Speaks a language our site does not support	
14)	Participant unable to read English	
15)	Participant already known to not to want to participate	
16)	Primary care doc or nephrologist known to not want pt to participate	
17)	Participant seems unable to be able to come to visits on his own and has no support	
18)	Enrolled or about to enroll in another intervention study	
19)	Lives so far away it did not seem useful to approach him	
20)	Plans to move to a new city	
21)	Incarcerated	
22)	Nursing Home or other institution	
	TOTAL NUMBER OF CANDIDATES NOT APPROACHED	

CHAPTER 51. COMBINE STUDY PARTICIPANT RECRUITMENT, SCREENING AND MANAGEMENT

51.1 Pre-Screening and Screening Procedures for the COMBINE Study

The inclusion and exclusion criteria for the COMBINE study define a specific patient population and protect ineligible individuals from unnecessary risks. Therefore, it is important to thoroughly investigate the patient's history and clearly document inclusion and exclusion criteria. Medical record review can be used for prescreening. Study staff should obtain Institutional Review Board's approval for these activities, as mandated by local practices.

Local laboratories will be used for lab tests to determine screening eligibility. The maximum time between the screening and the first baseline (B0) visit will be 1 calendar month. COMBINE Screening Form 107 is completed and key entered for each person who consents to the study. Additional screening visit forms are listed in the COMBINE Forms completion schedule:

https://qhsapps.ccf.org/ckdp/open_webdocs/Forms/FormsScheduleCOMBINE.pdf

51.2 Tracking Participants who are Approached but do Not Consent

Centers need to keep a listing of why the participant who was told about the study decided not to participate. These reasons are recorded on "The Reasons Why Participants who are Approached and do not Consent" tally sheet. The DCC will ask for each sites tally sheet prior to every Steering Committee Meeting.

51.3 Screening Visit

Participants will be scheduled to attend the screening visit. During the visit, the following procedures will be done:

- 1) Review protocol and obtain informed consent.
- 2) Review all prescreening data with the participant.
- 3) Review medical and medication history.
- 4) Obtain vital signs, including blood pressure, heart rate, height and weight. Blood pressure should be measured 3 times, one minute apart, and the mean of the second and third measure will be considered the visit blood pressure.
- 5) Obtain blood samples to be processed at Local Lab for measurement of electrolytes, BUN/creatinine, parathyroid hormone, serum phosphorus, serum glucose, total blood count, LFT, and CK.
Note: Forms 115 and 116 local labs can be used to report existing lab results up to 45 days prior to the screening visit date. The appropriate form must be entered for each collection date. Do not combine all results on one lab form if they were drawn on separate dates.
- 6) Perform a urine (or serum) pregnancy test for women of child-bearing potential.
- 7) Review the MRI safety questionnaire with the participant. (Disregard if participant did not consent to completing cardiac and bold renal MRIs.)
- 8) Review daily meal frequency.
- 9) Make arrangements for review of screening labs and for scheduling the next visit according to local practices.

51.4 Review of medications during the Screening Visit

All medications that the participant is currently taking should be reviewed at the screening visit for eligibility purposes.

Eligibility criteria states "Use of immunosuppressive medications. (This criterion excludes anyone who has received a solid organ transplant. Stable oral steroids \leq 10 mg of prednisone/day or inhaled steroids are exempted.)"

The participant is exempted if they are on a stable oral steroid <10 mg of prednisone/day or inhaled steroids or an equivalent. The following corticosteroids can be taken by the participant and would not be an exclusion:

Prednisone 10 mg is equivalent to:

- Cortisone 50 mg
- Hydrocortisone 40 mg
- Prednisolone 10 mg
- Methylprednisolone 8 mg
- Dexamethasone 1.5 mg

As long as the dose is less than noted above, the participant meets this criterion.

51.5 Baseline Procedures for the COMBINE Study

The complexity of the protocol suggests that an assessment of adherence prior to randomization would be useful. Therefore, eligible participants will be asked to provide evidence that they can take study medications during the 2-week run-in period. To be considered a good candidate for COMBINE, participant compliance with baseline study medications during the run in should be at least 80%. Baseline visits forms are listed in the COMBINE Forms completion schedule on the database study website.

51.6 Maximum Time Allowed Between Screening to Baseline 0

The Screening Visit date to the B0 visit can be no longer than 1 calendar month. B0 officially begins when the participant is given his or her study medications at the B0 visit. If more than 1 calendar month from Screening to B0 has occurred, the participant is excluded and may restart baseline. See section regarding “Re-Screening a Previously Enrolled Participant.”

51.7 Maximum Time Allowed Between B0 and Randomization

The participant can be randomized up to 6 weeks or 42 days from the B0 visit date. If more than 42 days from B0 to Randomization has occurred, the participant is excluded and may restart baseline. See section regarding “Re-Screening a Previously Enrolled Participant.”

51.8 Baseline Visit Windows

It is expected that patients will be randomized within 3 weeks of the B0 visit. If necessary, patients can be randomized up to 6 weeks (42 days) after B0.

51.9 Re-Screening a Previously Enrolled Participant

If a participant who was previously enrolled becomes ineligible during Baseline, a Form 163 Baseline Dropout Form needs to be entered. The participant may restart the Screening process seven days from the date the Form 163 Baseline Dropout Form was entered. This allows the study team to evaluate the circumstances surrounding the reason(s) participant was unable to be randomized within the allotted time. The center should notify the DCC if they plan on restarting the participant at a later date.

Form 403 - Re-Enrollment of a Previously Enrolled Participant Form (COMBINE) needs to be completed and the instructions on the form closely followed by the center. This form is then scanned or faxed to the DCC. This will show the intent of re-enrolling the participant. When a participant is rescreened and re-enters Baseline, all new baseline data (except for the MRI) are collected. MRI results can be used up to six months from the date of the MRI. Centers will need to check with their local IRB to see if the participant needs to sign a new consent when re-enrolling into the study.

The DCC will be in constant communication with the site during this process as the old data is moved and stored in a separate area of the database. When this has happened and the seven days have passed since Form 163 has been entered, and the DCC gives the approval, the participant can restart Baseline.

Important: the participant will keep the same identification number and alpha code for the duration of this UO1 CKD Consortium. The participant will repeat screening and baseline measures/forms to assure that the participant still meets all inclusion and exclusion criteria.

51.10 Baseline Visits

At each baseline study visit, blood samples will be collected. Whenever blood is drawn, time of day will be recorded. Prior studies have shown that assessment of the effects of dietary phosphate restriction on serum phosphate levels were masked if serum phosphate measurements were done in the early morning. In contrast, assessments in the mid-afternoon allowed for detection of a change in serum phosphate levels following interventions.

It is recommended:

- a. Serum collections are conducted between noon and 6:00 pm.
- b. Clinic appointments held in the afternoon to maximize detection of the effect of the intervention on serum phosphate levels and minimize influence of circadian changes. Ability to come in for afternoon appointments is not an absolute requirement for study participation. Participants who conduct both of their baseline visits in the morning due to necessity will be categorized as morning participants. Study coordinators will schedule their follow-up visits at about the same time as their baseline visits were held to minimize effects of circadian rhythm on longitudinal changes in phosphate and FGF23.

51.11 B0 Visit

During the B0 visit, the following procedures will be done:

- 1) All data collected during screening will be reviewed.
- 2) Provide the participant with a 24-hour urine collection container and collection aide, if needed. Instruct the participant how to accurately collect urine for 24 hours. To make sure that the participant understands how to do this, ask him to repeat back to you the instructions for the collection. Provide written instructions to take home with them along with the container (see Section 54, 24-Hour Urine Collection instructions. Ensure that the participant knows how to get in touch with COMBINE study staff members in case he/she has a question. A participant may be provided with more than one 24-hour urine container.
- 3) Ask the participant to complete a questionnaire about gastrointestinal (stomach) symptoms.
- 4) Distribute study medications and instruct the participant on how to take them.
- 5) Instruct the participant to bring the study pill bottles back to the next visit.
- 6) Make arrangements for scheduling the next visit according to local practices.
- 7) For a participant who is complying with study requirements up to this point, and who agrees to have the cardiac and renal MRIs done, personnel should schedule the scans to occur before the B2 Visit.

51.12 B1 Visit (1 week after B0)

During the B1 visit, the following procedures will be done:

- 1) The participant will bring in their first 24-hour urine collection. This sample will be used to measure 24-hour urine phosphorus, calcium, and to determine kidney function, creatinine and urea nitrogen. This urine is processed by the study coordinator and shipped to the Spectra Central Lab (see Spectra Chapter of the MOP). If the participant consented to have blood and urine stored at the NIDDK Biorepository, ship the urine collected for this visit according to the instructions provided in the Biorepository MOP Chapter.

- 2) Obtain vital signs, including blood pressure, heart rate, and weight. Blood pressure should be measured 3 times, one minute apart, and the mean of the second and third measure will be considered the visit blood pressure.
- 3) Draw about 4 tablespoons (60 mLs) of blood to measure FGF23, electrolytes, BUN, creatinine, glucose, albumin, parathyroid hormone, calcium and phosphorus levels.
- 4) If the participant agrees, obtain additional blood samples (30 mLs, 2 tablespoons) and urine samples to send to the NIDDK repository.
- 5) Ask the participant to provide a random urine sample. This sample will be used to test urine phosphorus, calcium, albumin, and creatinine.
- 6) The participant will have serum and whole blood drawn
- 7) Provide the participant with a container for the second 24-hour urine collection and instructions. Once again, ensure that the participant can clearly describe back to you how to collect urine for 24 hours.
- 8) The participant will bring their study medication pill bottles so that pill counts could be performed.
- 9) The participant will receive information about keeping a low phosphorus diet and how to avoid food items high in phosphorus.
- 10) The participant will fill out a questionnaire about any gastrointestinal (stomach) symptoms, about the ability to take the study drugs, and to assess for any potential side effects of the study drugs.
- 11) Arrangements for scheduling the next visit will be made according to local practices.

51.13 B2 Visit (2 weeks after B0)

During the B2 visit, the following procedures will be done:

- 1) The participant will bring in their second 24-hour urine collection. This sample will be used to measure 24-hour urine phosphorus, calcium, and to determine kidney function, creatinine and urea nitrogen.
- 2) Obtain vital signs, including blood pressure, heart rate, and weight. Blood pressure should be measured 3 times, one minute apart, and the mean of the second and third measure will be considered the visit blood pressure.
- 3) Draw about 3 tablespoons (45 mLs) of blood to measure FGF23, serum phosphorus, electrolytes, BUN/creatinine, glucose, parathyroid hormone, uric acid, hemoglobin A1c level, and calcium levels.
- 4) If the participant agrees, obtain additional blood (30 mLs, 2 tablespoons) and urine samples to send to the NIDDK repository.
- 5) The participant will provide a random urine sample. This sample will be used to test urine phosphorus, calcium, albumin, and creatinine.
- 6) The participant will have serum drawn
- 7) The participant will bring their study medication pill bottles so that pill counts could be performed.
- 8) The participant will receive information about keeping a low phosphorus diet and how to avoid food items high in phosphorus.
- 9) The participant will fill out a questionnaire about any gastrointestinal (stomach) symptoms, about ability to take the study drugs, and to assess for any potential side effects of the study drugs.
- 10) The participants can be randomized if the “Ready to Randomize Report” shows that the participant is eligible to be randomized (this is also described in the Randomization Section).
- 11) Arrangements for scheduling the next visit will be made according to local practices.

51.14 F0 Visit

The F0 visit is the name of the visit where the participant has given their first bottles of randomized study medications. If the F0 visit is on the same day or within 1 week of the B2 visit and there were no hospitalizations or other SAEs, then only complete Form 248 (Follow-Up Initial Pill Dispensing). If the FV0 visit is more than 1 week from the B2 visit and/or the participant was hospitalized or did have an

other SAE, then Forms 203 (Visit), 248 (Follow-Up Initial Pill Dispensing) and 285 (GI Symptoms and Other AEs) will need to be completed.

51.15 Dietary Information

At each visit, participants will receive education from the coordinators regarding efforts to reduce dietary phosphate intake. The information will include:

- a) instructions on how to read food labels in order to avoid foods with phosphate additives;
- b) advice to reduce serving sizes of animal protein;
- c) encouragement of consumption of vegetarian sources of protein instead of animal protein;
- d) advice to reduce consumption of dairy, and e) encouragement of consumption of egg whites instead of egg yolks.

Patient education materials have been developed to facilitate this instruction. These materials should be reviewed at each study visit.

51.16 Randomization Procedures for the COMBINE Study

Participants meeting eligibility criteria, having given their informed consent and successfully collected the required data and completed the run-in period will be eligible for randomization. Baseline cardiac and renal MRI studies should be completed prior to randomization but can take place up to two months following randomization. When the “Ready to Randomize Report” shows that the participant is eligible to be randomized, the study coordinator can then randomize the participant. The participant should receive the first bottles of blinded study medication as soon as possible post randomization.

Participants will be randomized to one of the following 4 groups:

- Lanthanum carbonate + nicotinamide
- Lanthanum carbonate + nicotinamide placebo
- Lanthanum carbonate placebo + nicotinamide
- Lanthanum carbonate placebo + nicotinamide placebo

51.17 General Issues of Follow-Up

At in-person visits, patient compliance to study drugs will be assessed either by questionnaire or pill count depending upon the visit (Table 1.8 of the Protocol). The study coordinator will reinforce instructions on dietary phosphate restriction. Concomitant medication therapy will be reviewed and updated at baseline, F3 and every 3 months thereafter. Information on adverse events (serious and non-serious) will be collected. The schedule of laboratory tests to be obtained during the in-person visits is listed in Table 1.8 of the Protocol. Additional blood samples will be collected and stored for future measurements. A GI symptoms form will be completed by questionnaire at each protocol visit. Blood pressure, heart rate and weight will be measured at all follow-up visits. Twenty-four hour urine specimens will be collected at some visits (Table 1.8 of the Protocol) to measure phosphate, calcium, urea, and creatinine. The 24-hour urine phosphate will be used as an indicator of dietary phosphate absorption and the 24-hour urea will be used as an indicator of dietary protein intake.

At each follow-up visit, participants will be counseled that they must not take any phosphate binders or multivitamins containing vitamin B3 in the form of niacin or nicotinamide in quantities greater than 100 mg/day. If a participant is taking a standard multi-vitamin tablet with < 100 mg/day of nicotinamide, the dose of the multivitamin may not be changed during the study period.

51.18 F12 MRI

Between F11 and F12 or upon withdrawal from study (for dialysis initiation or preemptive transplantation), participants will undergo cardiac and renal MRI. The cardiac and BOLD renal MRI may occur anytime between F11 and 2 weeks after F12 or at the time of early discontinuation prior to initiation of renal replacement therapy. If a participant withdraws from the study within 6 weeks of their baseline MRI

studies, discontinuation MRI studies will not be performed. MRIs should not be obtained in participants who have started dialysis or have been transplanted. Participants who have a contraindication to the MRI (i.e. pacemaker) will not undergo MRI studies but will continue to undergo all other study procedures.

Follow up visits forms are listed in the COMBINE Forms completion schedule located on the study website.

51.19 F12 Pill Counting Form 249

Form 249 (Follow-Up Pill Dispensing and Counting Form-COMBINE) should be completed as follows for the F12 visit (end of study):

Q6 (Visit number intended) = F12

Q7a –g should be entered with appropriate pill count information.

Q7j (# of “returned” bottles dispensed) should = 0 (since no “returned” bottles should be dispensed)

Q7k (COMBINE meal pattern planned for after this visit) = this should be whatever the patient says that their meal plan will be after they leave this visit

Q7l (# new bottles dispensed) = 0 (no new bottles should be dispensed)

Q7n (Prescription type) = 0 (Prescription discontinuation required per protocol)

Q7o (Prescribed # of pills per day as participant leaves this visit) = 0 (since the participant should not continue study meds after this visit)

Q8a and 8b will be blank since the participant is now off of study medications due to end of the study.

Q9 and Q10 will be blank since no bottles of study medications are dispensed

51.20 Follow-up Visits and Windows

In person follow-up visits will occur monthly for first 3 months after Randomization and every 3 months from month 3 until month 9. There will be a two month interval between month 9 and 11, and finally a 1 month interval between month 11 and 12 (Table 1). Additional visits will be held as needed at the discretion of the site investigator and study team members. All visits will be documented in the study database.

Timely visit adherence should be encouraged. The following windows are recommended:

- The window for monthly follow up visits is +/- 7 days.
- The window for visits that occur every 3 months is +/- 14 days.
- The window for MRI visits is +/- 14 days.

51.21 Priority of Requirements for Passive or Partially Compliant Participants

Once a participant is randomized, the center will need to continue to follow the participant. If the participant at any time states that they no longer want to participate or does not want a specific study procedure done, the Principal Investigator should speak with the participant. If at the end of the discussion, the participant still does not want to be in the study or does not want a specific study procedure done, then complete all data that the participant is willing to complete. It is important that communication with the participant continue. It may be that the participant will return to full procedure capabilities after a period of rest.

51.22 Pill count requirements for this protocol

We will monitor adherence with pill counts and by asking participants whether they are taking each medication regularly, irregularly, or not at all (Visit Form 203; https://clinicalresearch.ccf.org/ckdp/open_webdocs/Forms/Form203.pdf).

Pill counts will be performed on the following visits: B1, B2, F1-F3, and F12. Participants will be encouraged to bring their pill bottles with them to every visit.

51.23 How to distribute drug

Centers will run the Bottle Assignment Report which will assign the bottles numbers that should be given to the participant. Bottles given to the participant will be reported on Form 148 during Baseline and Form 248 and Form 249 during Follow-Up.

Once a bottle has been assigned to a participant it can never be reassigned to be used by a different participant. If these bottles were assigned to a participant during baseline, and the participant did not need them during baseline, and the participant has now been randomized, the bottles can be discarded. If this occurred during Follow-Up where the participant was randomized and bottles were assigned but not given to the participant, then the bottles can be held and dispensed to the participant the next time he or she needs pills.

It is important that the pill dispensing and counting forms be entered within 3 business days so that study medication inventory can be closely monitored.

51.24 Emergency resupply of drug

The DCC will monitor the study medication supply at each site and will order more study medications as needed.

The DCC will notify the site when medication has been ordered and sites should notify the DCC via email when the supply has been received.

51.25 MRI Visits Procedures

Each participating clinical center will be provided with a detailed imaging protocol and will be required to submit qualifying studies for certification by the MRI Cores prior to enrolling participants. All cardiac and renal MRI results will be captured according to pre-specified protocols, sent to and stored at the Cardiac MRI Core at Northwestern University. All cardiac MRI Core results will be read by the Cardiac MRI Core at Northwestern University. All renal MRI results will read by the Renal MRI Core at NorthShore.

Participants who have a contraindication to the MRI (i.e. pacemaker) will not undergo MRI studies but will continue to undergo all other study procedures.

Baseline cardiac and renal MRI studies need to take place prior to randomization. After participants meet all inclusion criteria, screening requirements and MRI safety criteria, pre-randomization cardiac and renal MRI will be obtained. These imaging studies could occur anytime between Baseline Visit 0 (B0) and prior to Baseline Visit 2 (BV2).

Between F11 and F12 or upon withdrawal from study (for dialysis initiation or preemptive transplantation), participants will undergo cardiac and renal MRI. The cardiac and renal MRI may occur anytime between F11 and 2 weeks after F12 or at the time of early discontinuation prior to initiation of renal replacement therapy. If a participant withdraws from the study within 6 weeks of their baseline MRI studies, discontinuation MRI studies will not be performed. MRIs should not be obtained in participants who have started dialysis or have been transplanted. Additional details are included in the MRI MOP Chapter (https://clinicalresearch.ccf.org/ckdp/open_webdocs/MOP/COMBINE%20MRI.pdf).

51.26 Management of Study Drug Doses during Follow-Up

During the first month following randomization (F0 to F1), randomized treatments will be started at lower doses. All participants will take one 750-mg nicotinamide or matched placebo daily.

Lanthanum carbonate or its placebo will be prescribed as follows:

Participants who eat 3 meals a day will take one 500 mg lanthanum carbonate or matched placebo with each meal (1500 mg).

Those who eat fewer than 3 meals a day will receive adjusted doses:

- Participants who eat 2 meals a day with no snacks will take one 500 mg lanthanum carbonate or matched placebo with each meal (1000 mg).
- Participants who eat 2 meals a day and one or more snacks will take one 500 mg lanthanum carbonate or matched placebo with each meal and one 500 mg lanthanum carbonate or matched placebo with a snack (1500 mg).

Lanthanum carbonate/placebo should be chewed not crushed or sucked. Participants who take lanthanum carbonate/placebo right after eating report less stomach upset.

For the remainder of the study (F1 through F12), randomized treatments will be taken at full doses. All participants will take nicotinamide 750 mg or matched placebo twice daily (1500 mg).

Participants who eat 3 meals a day will take two 500-mg lanthanum carbonate or matched placebo with each meal (3000 mg).

Those who eat fewer than 3 meals a day will receive adjusted doses:

- Participants who eat 2 meals a day with no snacks will take two 500-mg lanthanum carbonate or matched placebo with each meal (2000 mg).
- Participants who eat 2 meals a day and one snack will take two 500-mg lanthanum carbonate or matched placebo with each meal and one 500 mg lanthanum carbonate or matched placebo with the snack (2500 mg).
- Participants who eat 2 meals a day and two or more snacks will take two 500-mg lanthanum carbonate or matched placebo with each meal and one 500-mg lanthanum carbonate or matched placebo with 2 snacks (3000 mg).

Medication-related adverse events may occur in COMBINE participants. These events may be either detected by lab work or may result from symptoms reported by participants.

Note that if a patient who has already gone through the protocol steps and reached a point where he or she was required to stop both of his or her study medications per protocol, it is no longer necessary for that person to repeat the lab tests that are considered medication related adverse events below.

51.27 Hypophosphatemia

If a study participant has a core lab serum phosphate level lower than 2.8 mg/dl at any visit, an extra visit should be held as soon as possible so the serum phosphate test can be repeated. This repeat lab will be the "action lab" for dose adjustments, regardless of the core lab serum phosphate level. The local action lab should be obtained as soon as possible, but must be obtained within 15 days of the core lab blood draw. In the event that the local action lab cannot be obtained, or is not available within 15 days, then the available core lab serum phosphate level becomes the action lab for dose adjustments.

If the action lab test demonstrates a serum phosphate level of 2.8 mg/dL or higher, the participant should continue on full dose medications until the next protocol visit.

If the serum phosphate level on the action lab test is between 1.5 and 2.7mg/dL, both study medications should be prescribed at half dose until the next protocol visit.

If the serum phosphate level is \leq 1.4 mg/dL on the action lab test, both study medications should be stopped until the next protocol visit.

At the next protocol visit, if serum phosphorus level is 2.8 mg/dL or higher, restart full dose of both study medications. If the serum phosphorus level remains between 1.5 and 2.7, keep participant on half dose until the next protocol visit. If the serum phosphorus level becomes \leq 1.4 mg/dL at the next protocol visit, the participant should not be prescribed any study medication until the subsequent protocol visit.

Participants with an action lab test of 1.5 md/dL or higher can enter into the same algorithm summarized above at any subsequent protocol visit. In contrast, participants with an action lab test of 1.4 mg/dL or lower require special consideration through the remainder of the trial. In such an individual, if a core lab serum phosphate is 2.8 mg/dL or higher at a subsequent protocol visit, both study medications should be restarted at half dose, and the doses of these medications should not be titrated above half dose throughout the remainder of the trial. If the serum phosphate level on a subsequent protocol visit core lab is 2.7 mg/dL or lower, the participant should return for a local action lab draw within 15 days, as summarized above. If the action lab is 2.7 mg/dL or lower, the participant should remain off both study medications until such time as their serum phosphate is 2.8 mg/dL or higher at a subsequent core lab measurement. Last, if a participant has previously had an action lab test \leq 1.4 mg/dL resulting in the need to hold their study medications at any point during the trial, and has a subsequent action lab test \leq 1.4 mg/dL again at any point during the remainder of the trial, this individual should be maintained off both study medications for the remainder of the trial. In such an individual, even if subsequent core or local action lab tests return to levels of 2.8 mg/dL at future visits, the study medications should not be restarted.

51.28 Hyperphosphatemia

If a study participant has a central serum phosphate level of 5.9 or greater, an extra visit should be held as soon as possible so the test can be repeated locally. If the local test confirms a serum phosphate level over 5.9 mg/dl, this is a treatment safety medication stop for both study medications. All visits and measurements will continue. If the patient has a primary nephrologist or primary care physician, it is recommended that he or she be notified about the hyperphosphatemia and management will be deferred to these providers.

51.29 Intolerable GI or other side effects

Form 249 and F250:

8. a. Regarding “Prescription type” in Item 7n for “Lanthanum/Lanthanum placebo” column, what is the primary reason the L prescription is reduced or stopped? _ _ _ , _ _ _ , _ _ _
(Codes are listed beginning on Page 3. Secondary and tertiary reasons may also be specified.)

- b. Regarding “Prescription type” in Item 7n for “Nicotinamide/Nicotinamide placebo” column, what is the primary reason the N prescription is reduced or stopped? _ _ _ , _ _ _ , _ _ _
(Codes are listed beginning on Page 3. Secondary and tertiary reasons may also be specified.)

If a participant develops GI or other side effects that he or she considers to be intolerable or that are considered intolerable by the site investigators, dose adjustment will be at the discretion of the site investigator. Appropriate actions may include reduction of the dose of lanthanum carbonate or its placebo and/or reduction of the dose of nicotinamide or its placebo.

Additional recommendations for managing COMBINE participants with GI side effects include:

- If a participant develops intolerable GI or other side effects while taking the study drugs at full doses, the dose adjustment will be at the discretion of the Investigator and will be based on clinical evaluation of the side effects.
- Appropriate actions may include
 - adjust the dose of lanthanum carbonate or its placebo;
 - reduce the frequency of nicotinamide or its placebo;
 - discontinue lanthanum carbonate or its placebo;
 - discontinue nicotinamide or its placebo;
 - adjust the dose of lanthanum carbonate or its placebo and reduce the frequency of nicotinamide or its placebo;
 - discontinue study drugs and their respective placebos.
- For the participants taking the study drugs at the reduced doses or reduced frequencies, if the intolerable GI or other side effects have resolved at the time of the Unscheduled Visit, the participant will resume treatment at full doses or frequencies.
- For the participants taking the study drugs at the reduced doses or reduced frequencies, if the intolerable GI or other side effects have not resolved at the time of the Unscheduled Visit, the study drugs will be held, and the subject will return for another Unscheduled Visit within 2 weeks.
- For the participants taken off study drugs for intolerable GI or other side effects, if the side effects have resolved at the time of the Unscheduled Visit, the study drugs will be restarted at the 50% reduced doses/frequencies and another Unscheduled Visit will take place within 2 weeks. If the side effects have resolved at the time of the next Unscheduled Visit, the participant will resume treatment at full doses/frequencies.
- For participants found to have liver function test (AST, ALT, total bilirubin, or alkaline phosphatase) or CK levels > 4 times the upper limit of normal without other identifiable cause, these laboratory visits will be repeated within one week at an Unscheduled Visit and if abnormalities are confirmed, the study agents will be stopped permanently.
- For participants found to have platelet count is < 100,000 with clinical signs of platelet dysfunction (bruising, bleeding, and petechiae) or < 75,000 without clinical signs, laboratory tests will be repeated within one week at an Unscheduled Visit and if abnormalities are confirmed, the study agents will be stopped permanently.
- In addition to the Unscheduled Visits, interim telephone follow up visits will also be used to determine if the study treatments should be reduced or stopped for intolerable GI and other side effects. Such telephone visits will be followed up with Unscheduled in person Visits.

51.30 Management of off-study drugs

- a) Tracking concurrent meds
- b) Concurrent meds to be discouraged in follow up

51.31 Clinical events

After randomization, a COMBINE participant may be hospitalized, during which clinical events may take place. These events require the completion of special forms. See Adherence reinforcement.

51.32 General issues of adherence

During a long study participants may have difficulties adhering to the protocol. Study staff can take several steps to maintain and enhance adherence and to prevent non-adherence. Each point of contact with participants should be used to ensure understanding of study procedures, to develop rapport and trust with participant and to create a positive experience. Both in person and telephone communications could be used for these objectives. Some participants may also want to correspond by email.

51.33 In-person visits

Each of the in-person visits, starting with the screening visit, is an opportunity to take a proactive approach to prevent non-adherence and loss to follow up. Ensure that all elements of study procedures, including medication adherence, are clearly understood. Ask participants to repeat back the information you provided to enhance understanding. Written instruction should be distributed to enforce adherence and patients should be encouraged to call back with questions. Written instructions will be available for the following:

- Dose and instructions of when to take study medications
- How to collect 24-hour urine collections
- Dietary information

The study website will contain samples of these documents.

51.34 Telephone calls

Frequent phone contact with participants will facilitate adherence with follow up visits and with study medications. Suggested frequency of phone call contact is listed below:

- Reminder phone calls one day prior to each study visit
- Reminder phone calls prior to due date of 24-hour urine collections
- Reminder phone call prior to MRI visits to remind participants to fast and to hold certain medications
- Check-up phone calls at least once (at the mid-point) between consecutive study visits

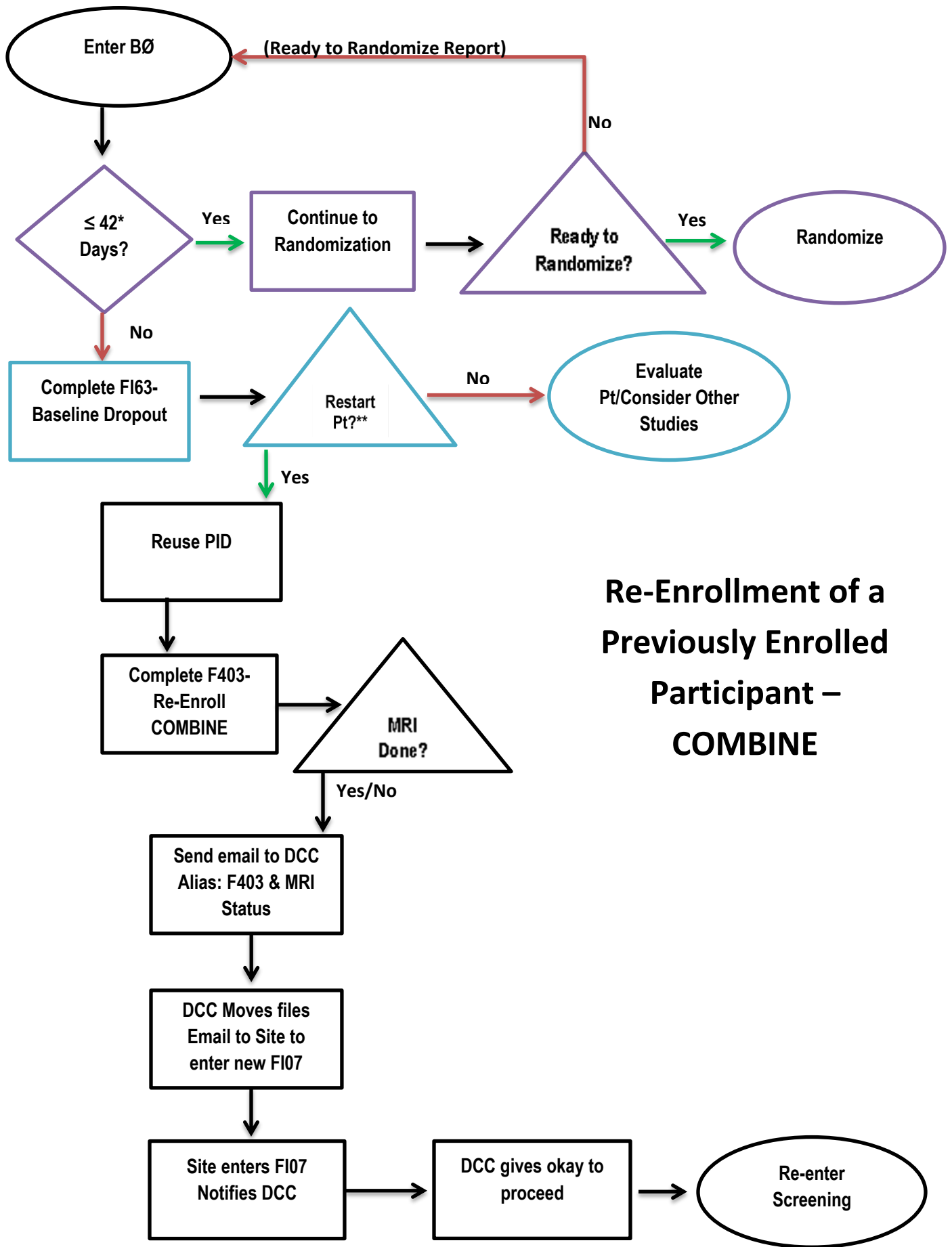
Other phone calls may include calls to return missed calls from participants and any phone calls in response to labs that necessitate scheduling an unscheduled visit.

51.35 Washout for those who complete COMBINE and want to start BASE

The washout period for COMBINE study medications is 1 month. Therefore, 1 month must have passed since the participant turned in their COMBINE study medications – that is, from the “Date pills counted or dispensed” (Q4) on Form 249 (Follow Up Pill Dispensing and Counting Form) where the “Prescription Type”(Q7n) = 0 (Prescription discontinuation required per protocol) for both Lanthanum/LP and Nicotinamide/NP.

Also, all data must be in the database. The Form 475 Study Closeout Form must be in the database and must show the “Date the PI determined no more data will be coming for this patient” (Q4).

Sites should notify the DCC via email at least one week prior to the planned BASE screening visit, since it will take about a week to confirm that all COMBINE data is in the database and take the steps needed to “convert” the participant from being an end of COMBINE participant to being a beginning of BASE participant. Participants will continue to use their same ID and alphacode for all CKD U01 studies, COMBINE, BASE or TarGut.



Re-Enrollment of a Previously Enrolled Participant – COMBINE

* If within B0 period but nearing end of baseline, daily email notices start 14 days prior to end of baseline.

**Participant can be restarted 7 days after Form 163 is entered into the database.

Natural Phosphorus Sources

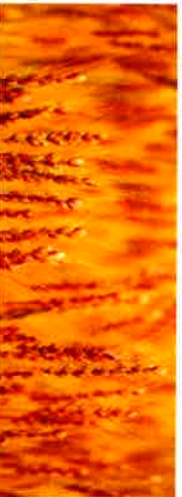
- Natural phosphorus sources are listed below.
- Many of these foods are considered “healthy” but they are higher in phosphorus and should be limited.
- You don’t need to completely avoid these, but do be careful with your portion sizes.

Animal Protein Beans/Legumes

Beef	Dry beans & peas such as black, pinto, or black eye
Pork	Lentils
Chicken	Lima beans
Turkey	Soybeans/edamame
Fish	Tofu
Shellfish	

Eggs & Dairy Grains/Nuts/Seeds

Egg yolk	Peanuts & tree nuts
Dairy milk	Seeds
All cheeses	Nut butters
Yogurt	Whole grain breads
Pudding	Whole grain side dishes
Custard/Flan	such as brown rice, quinoa, & whole wheat pasta
Ice Cream	



What Else Can I Eat?

- Smaller portions of meat, poultry. Choose ones labeled as “minimally processed”.
- Lots more vegetables, less animal foods. Try stir-fries.
- Add salads. Make them bigger. Eat them more often.
- More fruit – fresh, canned, frozen
- Egg whites
- Heart healthy oils (olive, canola, safflower, flaxseed)
- White rice & pasta (no **PHOS** additives in sauce).
- Water, tea, flavored waters & clear soft drinks without **PHOS** ingredients

Best Bets at Restaurants

- Pasta dishes without cheese or creamy sauces
- Asian dishes with less meat, more vegetables
- Hamburgers without cheese or bacon
- Breakfast sandwich on English muffin without cheese
- 6” instead of 12” subs. Add a salad
- Pizza - 1 slice without processed meat. Go easy on the cheese. Add a salad

COMBINE TRIAL

Dietary Phosphorus Quick Start



COMBINE TRIAL



Overview

The COMBINE pilot study tests the ability of 2 medications to lower phosphorus and certain hormones in your blood. The phosphorus in your diet can impact your blood phosphorus levels.

Phosphorus is a required mineral in your diet, but it is easy to eat more than your body needs. Excess phosphorus must be removed by your kidneys and intestines. This can damage your kidneys further. When the extra phosphorus you eat cannot be removed, the level rises in your blood, causing other hormones to increase. Your body must work harder to maintain mineral and hormone balance. These changes may cause damage to your heart, blood vessels, kidneys and bones.

We are going to teach you how to make changes in your diet to avoid or limit extra phosphorus.

What Foods Contain Phosphorus?

There are both **ADDITIVE** and **NATURAL** sources of phosphorus.

It is important to **AVOID** additive sources and **LIMIT** natural sources.

What are Added Sources of Phosphorus?

Convenience, processed and packaged foods often contain phosphorus additives. Use caution with restaurant foods. Avoid meats & poultry “enhanced” with solution or broth.



Search Ingredient Lists for PHOS

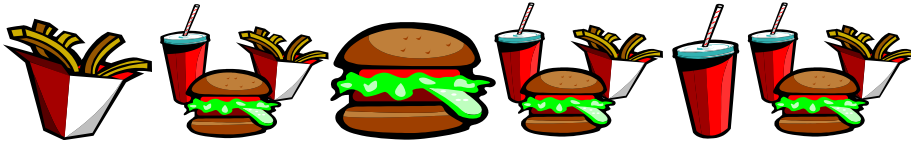
Phosphorus additives have long chemical names. Luckily you can find most of them if you search for the letters PHOS in the ingredient list. Here are just a few examples:

- Sodium phosphate
- Tricalcium phosphate
- Monosodium phosphate
- Sodium hexametaphosphate
- Also avoid *modified food starch*

What Foods have Phosphorus Additives?

Carefully review the labels of the following types of foods for phos:

- Prepared frozen foods
- Dry food mixes (macaroni & cheese, flavored noodles)
- Packaged meats, hot dogs, sausages
- Baked goods (biscuits, muffins)
- Soups
- Yogurts
- Colas, many sports & juice drinks
- Frozen vegetables with sauce
- Processed cheeses



Fast Food Choices

In general, it is best to limit fast food due to the use of **phosphorus** additives and high sodium content.

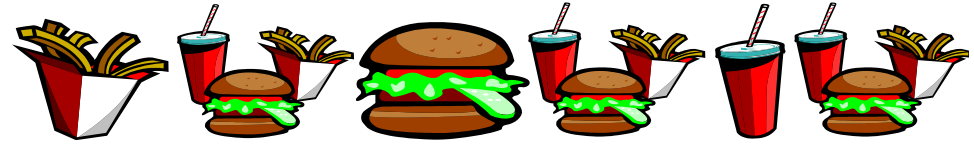
If you must have fast food, select “Better Choices”. Be prepared. Read ingredient information posted on the internet or at the restaurant in advance when possible.

Better Choices

- 6 inch sub/hoagie without cheese. Add lots of vegetables; select lower fat meats such as turkey and ham.
- Hamburger, no cheese
- 1 slice pizza and side salad. Ask that they go easy on the cheese. Add veggies.
- ½ serving Asian entrée with white rice. Choose lots of vegetables. Vegetarian options are best.
- Entrée-sized salad without cheese. Add lots of vegetables.

Poor choices

- Chicken, fried or grilled
- American cheese on anything
- Multiple slices of pizza. Avoid extra meat.
- Taco salads
- Roast beef sandwiches
- Large portions of Asian foods; especially with chicken or beef
- Hot dogs, polish boys, sausage



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- Taco salads
- Roast beef sandwiches
- Large portions of Asian foods; especially with chicken or beef
- Hot dogs, polish boys, sausage

Arby's

- The following items from Arby's contain phosphorus additives:

Roast Beef	Mozzarella sticks
Ham	Scrambled eggs
Bacon	French toastix
Chicken	Biscuits
Corned Beef	Sourdough breakfast
Roast Turkey	cheddar bread
Fish Fillet	Ciabatta bread
Wraps	Cream of broccoli soup
Cheddar cheese sauce	Buttermilk dressing
Potatoes/Fries	Chocolate cookie
Jalapeno bites	Milk shakes
Onion petals	Cola beverages

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

Boston Market

- The following items from Boston Market contain phosphorus additives:

Beef/BBQ Brisket
Crispy Country Chicken
Ham
Boston Carver sandwiches – all
Coleslaw
Macaroni & cheese
Mashed potatoes
Vegetable stuffing
Cornbread
Chocolate chip fudge brownie
Chocolate cake

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

Bruegger's Bagels

- The following items from Bruegger's Bagels contain phosphorus additives:

Cream cheese (all flavors)
Asiago parmesan bagel
Sourdough bagel
Asiago softwich
Plain softwich
Spinach & cheddar omelet sandwich
Wraps
Chicken (all products)
Roast beef
Turkey
Ham
American cheese
Fire roasted tomato soup
Four cheese broccoli soup
New England clam chowder
Hot chocolate

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

Burger King

- The following items from Burger King contain phosphorus additives:

Buns (except BK Shots)

Chicken

Fish

Bacon

Ham

All Potatoes/Fries

Onion rings

Kraft Macaroni and Cheese

French toast sticks

Biscuits

Pancakes/Syrup

Tortillas

Cini-Minis

Croutons

Cheese

Milk shakes

Hershey's sundae pie

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

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Dairy Queen

- The following items from Dairy Queen contain phosphorus additives:

Sandwich buns (all)

Hot dogs

Fish

Shrimp

Chicken

Turkey

BBQ beef

Quesadillas

Iron grilled cheese sandwich

French fries

Onion rings

Texas toast

Gravy

American and jack cheeses

Moolattes

Butterscotch and caramel toppings

Oreo brownie earthquake

Pecan mudslide

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

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Domino's

- The following items from Domino's contain phosphorus additives:

Deep dish crust
Thin crust
Bacon
All Chicken/Wings
Ham
Beef
Sausage
Philly meat
American cheese
Cheddar cheese sauce
Chicken alfredo
Chicken carbonara
Pasta Primavera
Garlic
Ranch dressing
Chocolate Lava Crunch Cake

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

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Dunkin' Donuts

- The following items from Dunkin' Donuts contain phosphorus additives:

Muffins
Donuts & "Munchkins"
"Fancies"
Danishes
Sticks
Biscuits
English muffin
Brownie
Hash browns
Sausage/Bacon/Ham
Breakfast wraps
All Sandwiches (Flatbread, Cravings, Deli, Favorites)
Chicken Caesar Salad
Soups
Reduced fat cream cheese
Cream (in coffee drinks)
Vanilla Bean, Coffee, & Tropicana Orange Coolattas
Hot chocolate (including white)
Dunkaccino
Vanilla chai

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

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KFC

- The following items from KFC contain phosphorus additives:

Chicken (all varieties)
Country Fried Steak
Fish
Pot Pie
Bacon
Sausage
All Potatoes
Macaroni and Cheese
Rice
Biscuits
Tortilla
Cornbread Muffin
Croutons
Cheese and Cheese
Sauce

Ranch Dressing and
Dipping Sauce
Parmesan Dressing and
Dipping Sauce
Cheetos
Strawberry Cream Pie
Sara Lee Pecan pie
Lemon meringue pie
Cookie Dough Pie
Sweet Potato Pie
Double chocolate chip
cake
Lil' bucket desserts

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

Long John Silver's

- The following items from Long John Silver's contain phosphorus additives:

All Battered Fish and Seafood

All Battered Chicken

Alaskan Flounder

Baked Cod Filet

Grilled Pacific Salmon

Popcorn Shrimp

Shrimp Scampi

All Bowl Meals

Breaded Clam Strips

Buttered Lobster Bites

Lobster stuffed Crab cake

French Fries

Hushpuppy

Rice

Broccoli Cheese Soup

Chocolate Cream pie

Pineapple Cream pie

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

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McDonald's

- The following items from McDonald's contain phosphorus additives:

Buns	Canadian bacon
Chicken	Granola
Fish	Hot caramel topping (for sundaes)
Bacon	Hot fudge topping (for sundaes)
French fries	Chocolate drizzle on coffee drinks
American cheese	Coffee creamer
Biscuits	Shakes
McMuffins	Cinnamon melts
McGriddles	Apple pie
Hotcakes	Vanilla ice cream
Hash browns	Cookies
Flour tortilla	
Eggs	
Breakfast steak	

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

Panera

- The following items from Panera contain phosphorus additives:

Focaccia breads
Cinnamon raisin bread
Honey wheat bread
Tomato basil bread
White Whole Grain bread
Apple Pastry, Cherry
pastry
Apple Cherry Cheese
Pastry Ring
Bundt cakes
Muffins & muffies
Scones
Bear claw
Cinnamon Roll
Cobblestone
Pecan Roll
Egg soufflés
Grilled breakfast
sandwiches
All Kid's Sandwiches
Chopped Chicken Cobb
Salad

All Paninis
Bacon Turkey Bravo
Sandwich
Italian Combo Sandwich
Mediterranean Veggie
Sandwich
Sierra Turkey Sandwich
Smoked Ham and Swiss
Sandwich
Tuna Salad Sandwich
Chipotle Chicken
Sandwich
Frozen Mocha and
Caramel beverages
Baked Potato Soup
Broccoli Cheddar Soup
Low Fat Garden Vegetable
Soup
New England Clam
Chowder

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

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Papa Johns

- The following items from Papa Johns Pizza contain phosphorus additives:

Alfredo sauce

Bacon

Chicken

Ham

Garlic parmesan sauce

Garlic ranch sauce

Blue cheese dipping sauce

Cheese dipping sauce

Garlic ranch sauce

Garlic parmesan sauce

Ranch dipping sauce

Chocolate dessert pastry

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

Pizza Hut

- The following items from Pizza Hut contain phosphorus additives:

Chicken wings
Ham
Pork
Beef
Bacon
Onion rings
Jalapeno poppers
Meatballs
Lite ranch dressing
Fat free ranch dressing
White pasta sauce

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

Subway

- The following items from Subway contain phosphorus additives:

Parmesan oregano bread
Italian herbs & cheese bread
Flatbread
Wraps
Chicken
Ham
Cold cut combo meats
Italian BMT meats
Roast beef
Seafood sensation
Steak
Subway club meats
Turkey
Bacon
American cheese
Ranch dressing
Fat Free Italian Dressing
Chipotle Southwest sauce
Fat free honey mustard sauce
Light mayonnaise

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

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Taco Bell

- The following items from Taco Bell contain phosphorus additives:

Flour tortilla
Chalupa shell
Flat Bread
Beef
Steak
Chicken
Chili
Nacho cheese sauce
Lava Sauce
Potato bites
Sour cream
Three cheese blend
Caramel Apple Empanada

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

Wendy's

- The following items from Wendy's contain phosphorus additives:

All Chicken/Wings

Bacon

Turkey

Ham

Buns and Rolls

American cheese

Frosty (all flavors)

French fries

Sour cream

Ancho chipotle ranch dressing

Cheddar cheese sauce

- These foods add phosphorus to your diet.
- Avoid menu items that consist of these foods.

Arby's

Better Choices

Main Dish

- None

Sides

- None

Desserts

- Apple Turnover
- Cherry Turnover

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September 11, 2014

Dear colleagues,

As you may recall, at the last faculty meeting we briefly introduced the upcoming COMBINE study. Below we provide some additional details.

The COMBINE study is a 12-month, randomized, double-blinded, four arm parallel study in 200 CKD stage 3–4 patients. The study will be conducted at six centers across the US. The overall goal is to investigate the effects of the interventions on changes in serum phosphate and FGF23 levels. An ancillary study will assess the impact of the interventions on cardiovascular, renal and bone measures.

We are looking to recruit patients with CKD stages 3 and 4 who are 18 years or older with the following:

- 1) eGFR 20-45 ml/min/1.73m²
- 2) serum phosphate levels \geq 2.8 mg/dL
- 3) platelet count \geq 125,000/mm³

Participants will be randomized to one of the following four groups:

- 1) lanthanum carbonate + nicotinamide
- 2) lanthanum carbonate + nicotinamide placebo
- 3) lanthanum carbonate placebo + nicotinamide
- 4) lanthanum carbonate placebo + nicotinamide placebo

During the study, participants will:

- 1) take the study medications
- 2) receive nutrition information
- 3) undergo blood and 24-hour urine tests
- 4) undergo 2 cardiac/renal MRIs (without contrast)

Participants could opt out of the MRI component and still participate in the study. Study visits occur once a month for the first 3 months followed by 4 additional visits 3 months apart. Participants will be compensated \$50 for each study visit and \$225 for each MRI visit. Parking and transportation expenses will be reimbursed.

Our research coordinators, Michelle Bradley and Gina Schwartz, will be coming to the Nephrology clinic to introduce the study to potentially eligible patients. Michelle and Gina will approach you prior to contacting the patients.

Thank you for your support.

Sincerely,



Myles Wolf, MD, MMSc



Do you see a doctor

A cartoon character of a kidney, colored red and yellow, with a smiling face, wearing blue gloves and shoes, and holding a stethoscope.

for kidney care?

You may be eligible for a **RESEARCH** study at Northwestern University on **YOUR KIDNEYS**



What is the purpose of the research study?

We want to test the effectiveness of **Vitamin B3** and **phosphorus binding** medication to lower **phosphorus** and **FGF23 hormone** in people with **Chronic Kidney Disease (CKD)**.

What do your kidneys do?

Healthy kidneys filter your blood. They remove wastes from your body. These wastes products are naturally made in your body and also come from the food you eat.

What is Chronic Kidney Disease (CKD)?

CKD develops when your kidneys do not remove waste properly. The waste build up in your blood and cause damage to your body.

What is Phosphorus and FGF23 hormone?

Phosphorus is a mineral found in bones in your body. People get phosphorus from the food they eat. **FGF23 hormone** "tells" the kidneys how much phosphorus to get rid of in the urine.

Phosphorus and CKD

In **CKD**, too much **phosphorus** builds up in the blood. This can lead to heart and bone problems.

Who is leading the study?

Kidney doctors at Northwestern University:

Myles Wolf, MD, MMSc, Principal Investigator

Tamara Isakova, MD, MMSc

Who can participate? NU IRB#: STU00089187

If you see a doctor for your kidneys, you may be eligible.

If I agree to participate, what will I do?

- Complete 11 visits at Northwestern University over 12 months:
 - 11 visits (30-60 minutes per visit)
- Give blood and urine samples
- You will receive information about lowering dietary phosphorus intake
- You may be asked to take a phosphorus binder (medication that binds to the phosphorus that you eat), vitamin B3, and/or a placebo
- You will have MRI scans of heart and kidneys
- Receive financial payments for your time and effort



How will I benefit?

- Help the future of CKD patient care

INTERESTED?

For more information, **please call**:

Michelle D. Bradley at 312-503-1909

Gina Schwartz at 312-503-3865

Your COMBINE Plate

Food choices can make a big difference in your phosphorus intake. Dividing your plate into sections can help you eat the right amount of phosphorus.



Eat your meals and snacks about the same time every day.



Do not skip meals.



Take study medications with each meal/snack as directed.

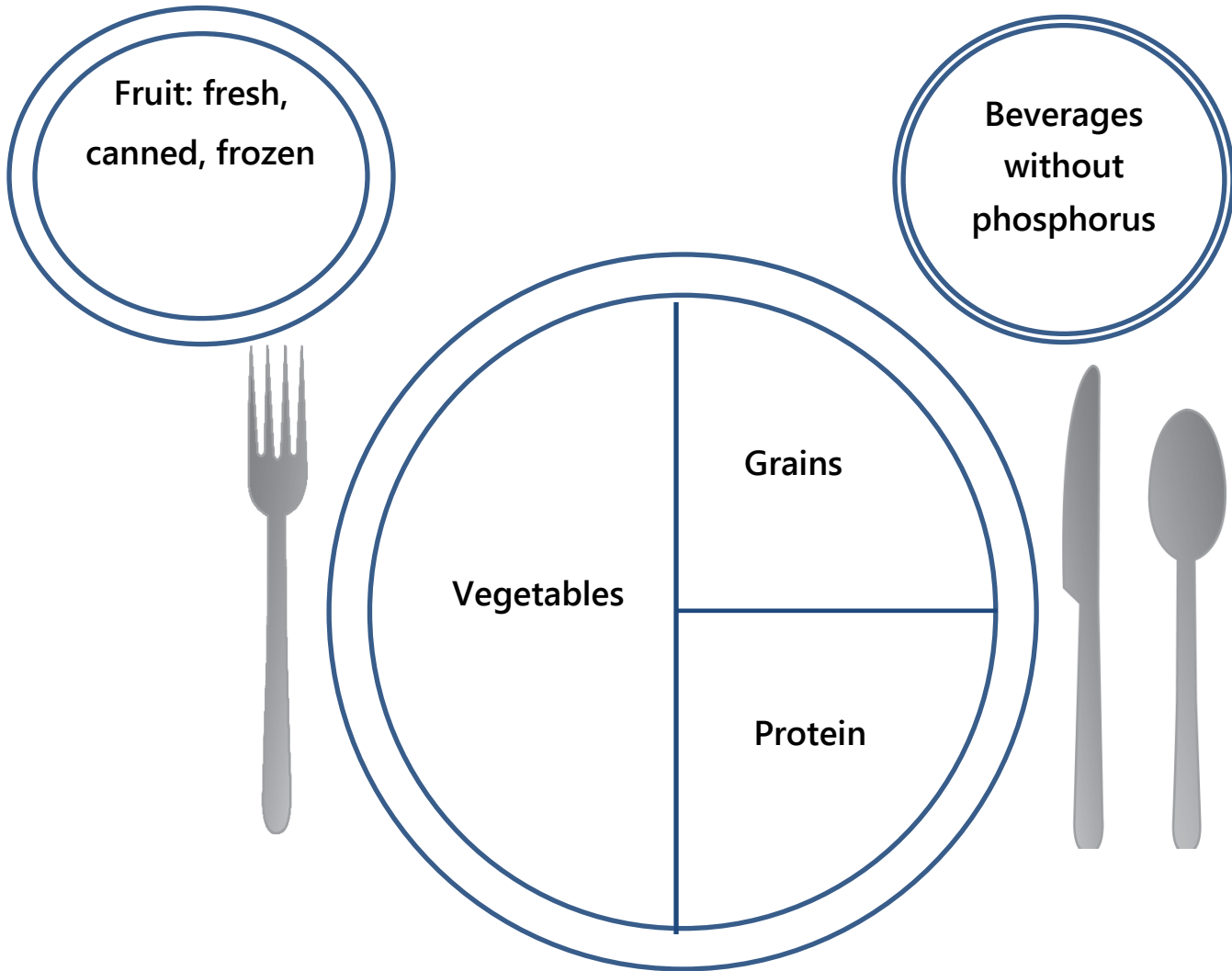


Limit foods that contain **phosphorus** additives.



Limit foods that are naturally high in phosphorus.

Your COMBINE Plate



Portion Out Your Plate

½ PLATE VEGETABLES: Fill half your plate with a colorful assortment of vegetables.

¼ PLATE PROTEINS: Smaller portions of meat, chicken and fish are better for you.

¼ PLATE STARCHES: Refined grains like white rice, regular pasta should be placed on this part of your plate as well as starchy vegetables like potatoes and corn

Effects of Nicotinamide and Lanthanum Carbonate on Serum Phosphate and FGF23 levels in patients with stage 3-4 Chronic Kidney Disease

(The Ckd Optimal Management with BInders and NicotinamidE: **COMBINE** STUDY)

Telephone Screening Script

Coordinator: Hello. My name is Michelle Bradley and I am the research coordinator working with Drs. Wolf and Isakova. A few weeks ago we mailed letters to patients of Northwestern University about a research study in people with kidney disease. Do you have a few minutes to discuss?

Patient: (1) If the patient responds **yes**, proceed to the comments listed below in section (a) for coordinator's response.

(2) If the patient responds **they do not have time right now to discuss**, proceed to the comments listed below in section (b) for the coordinator's response.

(3) If the patient responds **they do not want to hear about the study**, proceed to the comments listed below in section (c) for the coordinator's response.

Coordinator: (a) The purpose of the research study is to test the effectiveness of vitamin B3 and phosphorus binding medication to lower phosphorus and FGF23 hormone in people who are receiving treatment for their kidneys. If you agree to participate you will complete 11 visits at the Northwestern University Prevention Medicine Clinic (located at the downtown Chicago campus) and two visits to the MRI clinic over 12 months. Each clinic visit is 30-40 minutes in duration and the two MRI visits take 90 minutes to complete. Participation in the study will require for you to (1) give blood and urine samples, (2) receive information about decreasing dietary phosphorus intake (3) take phosphorus binders, vitamin B3, and/or a placebo (4) have two MRI (no contrast) scans of the heart and kidneys. For your participation in the study, you will receive \$50 for each study visit completed, \$225 for each MRI scan completed, for a total of \$1000. Does this study sound like something you would be interested in participating?

(b) **What would be a better time?** I would be willing to call during a mutually convenient time. (Coordinator should proceed with setting a phone appointment with patient that is more convenient and make plans to call during this time).

(c) **We will note you do not want to receive any further information on this study.** We will remove your contact information from our study recruitment contact file so you will not receive any further phone calls about this study. Thank you so kindly for your time.

Patient: (a) Are there **any benefits for participating** in this research study?

Coordinator: (a) **There are no direct benefits for your participation in the study.** However, the information gained from this study will be used to improve treatment for patients with chronic kidney disease.

Patient: (a) Can I get more information on the study?

Coordinator: (a) Yes. Would it be possible to schedule a screening visit? I can provide more detailed information at the screening visit. If you believe the study is a best fit for you, we can move forward with the study screening process. There is no obligation to participate in the study.



SNACKS

Everyone wants a snack now and then! Snacks are a good opportunity to add nutrition to your total day's food intake. Instead, snacks are often full of empty calories and **phos**phorus additives. The foods you decide to eat are choices. Treat your body well and make them "Smart Snacks". Always read package label ingredient lists to avoid **phos**phorus additives.

Smart Snacks

- Fruit or fruit salads. Try something different this week! Kiwi, mango, watermelon, cantaloupe, honey dew, oranges, tangerines, apples, pears, grapes.
- Bowl of strawberries, blueberries &/or raspberries with real whipped cream (read ingredient label for **phos**).
- Raw vegetables with or without dip or nut butter. Keep a raw vegetable platter in your refrigerator at all times. Vary the offerings to include carrots, celery, snow pea pods, cucumbers, bell peppers, grape tomatoes, broccoli, cauliflower and summer squash.
- Fruit popsicle
- Sorbet
- Lite popcorn
- Homemade fruit and vegetable smoothies. There are many recipes on the internet.
- Hardboiled egg whites

In Moderation

- Snack crackers or chips without **phos** ingredients
- Yogurt, without extra added calcium or **phos** ingredients



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- Hardboiled egg whites

In Moderation

- Snack crackers or chips without **phos** ingredients
- Yogurt, without extra added calcium or **phos** ingredients

Food Products Commonly Containing Phosphorus Additives

Read ingredient labels to find phosphorus additives. Phosphorus additives are commonly added to ready to eat foods such as:

- Meats/ Poultry/ Seafood
 - Processed items such as chicken nuggets, hot dogs, deli meats, crab
 - Items enhanced with a broth solution such as quick frozen chicken, turkey
- Bakery products
 - Biscuits, snack cakes
- Cheeses
 - Processed and spreadable cheeses
- Instant products
 - Puddings, sauces
- Beverages
 - Colas, flavored waters, fruit drinks

Can you find the phosphorus additives in the ingredients?

Ingredients: Enriched macaroni product (wheat flour, niacin, ferrous sulfate [iron], thiamin mononitrate [vitamin B1], riboflavin [vitamin B2], folic acid), cheese sauce mix (whey, milkfat, milk protein concentrate, salt, calcium carbonate, sodium tripolyphosphate, contains less than 2% of citric acid, sodium phosphate, lactic acid, milk, yellow 5, yellow 6, enzymes, cheese culture)

Hidden Phosphorus in the Diet

- Limit high phosphorus foods such as dairy, whole grains, dry beans, nuts and colas
- Most people are not aware of the sources of phosphorus additives in foods
- Convenience foods, ready to eat and processed foods frequently contain phosphorus additives
- Read ingredient labels to find phosphorus additives such as:

Dicalcium phosphate
Disodium phosphate
Monocalcium phosphate
Monosodium phosphate
Potassium tripolyphosphate
Pyrophosphate
Sodium acid pyrophosphate
Sodium aluminum phosphate
Sodium hexametaphosphate
Sodium phosphate
Sodium triphosphate
Tetrasodium pyrophosphate
Tricalcium phosphate
Trisodium triphosphate

CHAPTER 53: COMBINE LABORATORIES OVERVIEW

Video: Overview of Laboratory Collection, Processing and Shipping Procedures

Please use the link to access the video via YouTube:

https://www.youtube.com/watch?v=kOv0rf_WO0g&feature=em-upload_owner

Please use the link to download the video from my google drive (in mpv format):

<https://drive.google.com/file/d/0B7cLUjcdBZtwaTJGTE9vcDhPUFk/view?usp=sharing>

COMBINE STUDY - SPECIMENS COLLECTION and SHIPPING GUIDE *as of 08/17/2015*

	Serum (sent to Spectra)	Serum for FGF23 (sent to UW)	Serum (sent to NIDDK Repository)	Plasma for FGF23 (sent to UW)	Plasma (sent to NIDDK Repository)	Whole Blood (sent to Spectra)	Spot Urine (sent to Spectra)	24-Hour Urine (sent to Spectra)	24-Hour Urine (sent to NIDDK Repository)
Collect:	<i>8.5 ml SST tiger top tube</i>	<i>8.5 ml SST tube</i>	<i>4ml SST gold top tube</i>	<i>4 ml lavender top tube</i>	<i>4.5 ml PST light green top tube</i>	<i>2 ml lavender top tube (EDTA additive)</i>	<i>Urine cup w special transfer needle, then 8.0 ml yellow top conical tube</i>	<i>Jug, then transfer 50 ml to urine cup w special transfer needle, then 8.0 ml yellow top conical tube</i>	<i>Jug, then transfer to 90 ml urine cup</i>
Form #	<i>F331</i>	<i>F329/330</i>	<i>F300</i>	<i>F329/330</i>	<i>F300</i>	<i>F331</i>	<i>F331</i>	<i>F335</i>	<i>F301</i>
Local Storage	<i>Fridge</i>	<i>-80° Freezer in box</i>	<i>Fridge</i>	<i>-80° Freezer</i>	<i>Fridge</i>	<i>Fridge</i>	<i>Fridge</i>	<i>Fridge</i>	<i>Fridge</i>
Ship on	<i>Cold pack</i>	<i>Dry ice</i>	<i>Cold pack</i>	<i>Dry Ice</i>	<i>Cold pack</i>	<i>Cold pack</i>	<i>Cold pack</i>	<i>Cold pack</i>	<i>Cold pack</i>
Ship Sample in:									
B1	<i>1 - 8.5 ml SST tiger top tube</i>	<i>2 - 2ml cryovials</i>	<i>1 - 4ml SST gold top</i>	<i>2 - 2ml cryovials</i>	<i>1 - 4.5 ml PST lt. green top</i>	<i>2 - 2 ml lavender top tubes</i>	<i>1 - 8.0 ml yellow top conical tube</i>	<i>1 - 8.0 ml yellow top conical tube</i>	<i>1 - 90 ml cup</i>
B2	<i>1 - 8.5 ml SST tiger top tube</i>	<i>2 - 2ml cryovials</i>	<i>1 - 4ml SST gold top</i>	<i>2 - 2ml cryovials</i>	<i>1 - 4.5 ml PST lt. green top</i>	<i>(2 - 2 ml lavender top tubes, if not collected at B1)</i>	<i>1 - 8.0 ml yellow top conical tube</i>	<i>1 - 8.0 ml yellow top conical tube</i>	<i>1 - 90 ml cup</i>
F1	<i>1 - 8.5 ml SST tiger top tube</i>	<i>2 - 2ml cryovials</i>	<i>-</i>	<i>2 - 2ml cryovials</i>	<i>-</i>	<i>1 - 2 ml lavender top tube</i>	<i>-</i>	<i>-</i>	<i>-</i>
F2	<i>1 - 8.5 ml SST tiger top tube</i>	<i>2 - 2ml cryovials</i>	<i>-</i>	<i>2 - 2ml cryovials</i>	<i>-</i>	<i>1 - 2 ml lavender top tube</i>	<i>-</i>	<i>-</i>	<i>-</i>
F3	<i>1 - 8.5 ml SST tiger top tube</i>	<i>2 - 2ml cryovials</i>	<i>1 - 4ml SST gold top</i>	<i>2 - 2ml cryovials</i>	<i>1 - 4.5 ml PST lt. green top tube</i>	<i>2 - 2 ml lavender top tubes</i>	<i>1 - 8.0 ml yellow top conical tube</i>	<i>1 - 8.0 ml yellow top conical tube</i>	<i>1 - 90 ml cup</i>
F6	<i>1 - 8.5 ml SST tiger top tube</i>	<i>2 - 2ml cryovials</i>	<i>1 - 4ml SST gold top</i>	<i>2 - 2ml cryovials</i>	<i>1 - 4.5 ml PST lt. green top</i>	<i>2 - 2 ml lavender top tubes</i>	<i>1 - 8.0 ml yellow top conical tube</i>	<i>1 - 8.0 ml yellow top conical tube</i>	<i>1 - 90ml cup</i>
F9	<i>1 - 8.5 ml SST tiger top tube</i>	<i>2 - 2ml cryovials</i>	<i>-</i>	<i>2 - 2ml cryovials</i>	<i>-</i>	<i>2 - 2 ml lavender top tubes</i>	<i>-</i>	<i>-</i>	<i>-</i>
F12	<i>1 - 8.5 ml SST tiger top tube</i>	<i>2 - 2ml cryovials</i>	<i>1- 4ml SST gold top</i>	<i>2 - 2ml cryovials</i>	<i>1 - 4.5 ml PST lt. green top</i>	<i>2 - 2 ml lavender top tubes</i>	<i>1 - 8.0 ml yellow top conical tube</i>	<i>1 - 8.0 ml yellow top conical tube</i>	<i>1 - 90 ml cup</i>



Laboratory Services Manual

Protocol: COMBINE Study Manual of Operations Chapter 54

1. General Information

Supplies

Supplies for the COMBINE Study will be provided by Spectra Laboratories. Start-up supplies will be sent to your site prior to the start of this clinical trial. Please check the visit type and use the appropriate visit kit. Study kits will be labeled with the kit name and expiration date for that kit. Please be aware of the expiration date of the study kit.

Should you need additional supplies at any point during this clinical trial, you can order more supplies using the reorder sheet found on the CKD website; faxing instructions to order additional supplies from Spectra are denoted on the reorder sheet.

Requisitions

Please use COMBINE mailing Form331-Serum/Whole Blood/Spot Urine Mailing and Form 335 - 24-hour Urine Mailing for each collection period, as appropriate.

Please complete ALL THE REQUESTED INFORMATION ENTIRELY and check the appropriate study visit. Be sure to add the appropriate barcodes to each mailing form (see pages 8-9) and keep a copy for your records.

Spectra Team

Please feel free to contact any of our dedicated team members if you have any questions regarding any lab issue. The team may be reached during the hours of 8:30AM and 6:00PM Eastern time at 1-800-517-7157 ext. 5330.

2. Safety Laboratory Sample Collection

Laboratory Kit Components:

COMBINE Kit for FGF23 – Important: See MOP Chapter 55 for proper processing and shipping to University of Washington. Barcodes provided by UW.		
88-3470-2	Cryovial, 2mL	4
88-3026-6	8.5mL Serum Separator Tube (gel barrier) (tiger top)	1
--	4mL Lavender top (EDTA additive)	1
--	Pipettes	2
87-0252-4	Clear Bag, Small	1

COMBINE Kit 3494: Use for Visit B2		
88-3126-6	Tube Holder	1
88-3044-4	Safety Needle	1
87-7283-1	23 G BUTTERFLY NEEDLE	1
88-3328-9	Study Barcode Code Labels	2
88-3042-2	Safety ‘Biohazard’ Research Bag	1
87-0734-4	Specimen Tray, small clear ‘LifePak’	1
87-0252-4	Clear Bag, Small	1
88-8025-5	Ice Pack	1
88-3354-4	Shipping Box printed with ‘Spectra Clinical Research’	1
88-3025-5	8.5mL Serum Separator Tube (gel barrier) (tiger top)	1
87-4989-8	Urine Chemistry Kit (4989) (urine cup, 8.0 mL yellow conical tube)	2
--	COMBINE kit FGF23	1

COMBINE Kit 3495: Use for Visits B1, (B2 if needed), F3, F6 and F12		
88-3126-6	Tube Holder	1
88-3044-4	Safety Needle	1
87-7283-1	23 G BUTTERFLY NEEDLE	1
88-3328-9	Study Barcode Code Labels	2
88-3042-2	Safety ‘Biohazard’ Research Bag	1
87-0734-4	Specimen Tray, small clear ‘LifePak’	1
87-0252-4	Clear Bag, Small	1
88-8025-5	Ice Pack	1
88-3354-4	Shipping Box printed with ‘Spectra Clinical Research’	1
88-3025-5	8.5mL Serum Separator Tube (gel barrier) (tiger top)	1
87-4989-8	Urine Chemistry Kit (4989) (urine cup, 8.0 mL yellow conical tube)	2
88-3027-7	2mL Lavender Top Tube (EDTA additive)	2
--	COMBINE kit FGF23	1

COMBINE Kit 3496: Use for Visits F1, and F2		
88-3126-6	Tube Holder	1
88-3044-4	Safety Needle	1
87-7283-1	23 G BUTTERFLY NEEDLE	1
88-3328-9	Study Barcode Code Labels	1
88-3042-2	Safety 'Biohazard' Research Bag	1
87-0734-4	Specimen Tray, small clear 'LifePak'	1
87-0252-4	Clear Bag, Small	1
88-8025-5	Ice Pack	1
88-3354-4	Shipping Box printed with 'Spectra Clinical Research'	1
88-3025-5	8.5mL Serum Separator Tube (gel barrier) (tiger top)	1
88-3027-7	2mL Lavender Top Tube (EDTA additive)	1
--	COMBINE kit FGF23	1

COMBINE Kit 3497 Use for Visit F9		
88-3126-6	Tube Holder	1
88-3044-4	Safety Needle	1
87-7283-1	23 G BUTTERFLY NEEDLE	1
88-3328-9	Study Barcode Code Labels	1
88-3042-2	Safety 'Biohazard' Research Bag	1
87-0734-4	Specimen Tray, small clear 'LifePak'	1
87-0252-4	Clear Bag, Small	1
88-8025-5	Ice Pack	1
88-3354-4	Shipping Box printed with 'Spectra Clinical Research'	1
88-3025-5	8.5mL Serum Separator Tube (gel barrier) (tiger top)	1
88-3027-7	2mL Lavender Top Tube (EDTA additive)	2
--	COMBINE kit FGF23	1

4L Urine Containers

4L urine containers will be provided by Spectra for 24-hour urine collections and will be shipped separately from the kits.

A preservative of **30 ml 6N hydrochloric acid** (which is about 20% HCL) will need to be ordered by center personnel and added to the urine container prior to giving the container to the participant. For the participant, the risk of injury from the hcl decreases as the container becomes filled with urine.

Collections should be as close to 24-hours as possible. Collection time should be between 20 and 28 hours. One of the collections during Baseline must be between 20 and 28 hours for the participant to be randomized.

3. Specimen Handling Instructions

Visit #	Kit #	Form #	SAMPLE	TEST	LABEL	INSTRUCTIONS
B1	3495	331	2-2mL EDTA Lavender top	PTH and HbA1c	Lavender on 1, Miscellaneous on the other	Do not centrifuge
			1-8.5 SST Tiger Top	Chemistry, Serology	SST Gel	Centrifuge
			Urine cup, yellow 8.0 conical tube	Spot urine tests	Urine Chemistries	Do not centrifuge
		335	Urine collection jug, urine cup, yellow 8.0 conical tube	24 hr. Urine tests	Urine Chemistries	Do not centrifuge
B2	3494 (use Kit 2 if whole blood not collected at B1)	331	<i>IF NOT DONE AT B1:</i> 2 -2mL EDTA Lavender top	<i>PTH and HbA1c</i>	<i>Lavender on 1, Miscellaneous on the other</i>	Do not centrifuge
			1-8.5 SST Tiger Top	Chemistry, Serology	SST Gel	Centrifuge
			Urine cup, yellow 8.0 conical tube	Spot urine tests	Urine Chemistries	Do not centrifuge
		335	Urine collection jug, urine cup, Yellow 8.0 conical tube	24 hr. Urine tests	Urine Chemistries- <i>Note: separate barcodes provided</i>	Draw from urine cup Do not centrifuge
F1	3496	331	1-2mL EDTA Lavender top	Hematology (CBC, Diff, Platelet)	Lavender	Do not centrifuge
			1-8.5 SST Tiger Top	Chemistry	SST Gel	Centrifuge
F2	3497	331	1-2mL EDTA Lavender top	Hematology (CBC, Diff, Platelet)	Lavender	Do not centrifuge
			1-8.5 SST Tiger Top	Chemistry	SST Gel	Centrifuge
F3	3495	331	2-2mL EDTA Lavender top	PTH and Hematology (CBC, Diff, Platelet)	Lavender on 1, Miscellaneous on the other	Do not centrifuge
			1-8.5 SST Tiger Top	Chemistry, Serology	SST Gel	Centrifuge
			Urine cup, yellow 8.0 conical tube	Spot urine tests	Urine Chemistries	Do not centrifuge
		335	Urine collection jug, urine cup, Yellow 8.0 conical tube	24 hr. Urine tests	Urine Chemistries- <i>Note: separate barcodes provided</i>	Draw from urine cup Do not centrifuge
F6	3495	331	2-2mL EDTA Lavender top	PTH and Hematology (CBC, Diff, Platelet)	Lavender on 1, Miscellaneous on the other	Do not centrifuge
			1-8.5 SST Tiger Top	Chemistry, Serology	SST Gel	Centrifuge
			Urine cup, yellow 8.0 conical tube	Spot urine tests	Urine Chemistries	Do not centrifuge
		335	Urine collection jug, urine cup, Yellow 8.0 conical tube	24 hr. Urine tests	Urine Chemistries- <i>Note: separate barcodes provided</i>	Draw from urine cup Do not centrifuge

F9	3497	331	1-2mL EDTA Lavender top	PTH	Lavender	Do not centrifuge
			1-8.5 SST Tiger Top	Chemistry	SST Gel	Centrifuge
F12	3495	331	2-2mL EDTA Lavender top	PTH, HbA1c and Hematology (CBC, Diff, Platelet)	Lavender on 1, Miscellaneous on the other	Do not centrifuge
			1-8.5 SST Tiger Top	Chemistry, Serology	SST Gel	Centrifuge
			Urine cup, yellow 8.0 conical tube	Spot urine tests	Urine Chemistries	Do not centrifuge
		335	Urine collection jug, urine cup, Yellow 8.0 conical tube	24 hr. Urine tests	Urine Chemistries- <i>Note:</i> <i>separate barcodes</i> <i>provided</i>	Draw from urine cup Do not centrifuge

Freeze Ice Packs the day before Blood Draw

Prior to Blood Draw

1. Call FedEx to schedule a pickup, if needed (some have standard pick-up)
2. Review guide for visit number and type of collection(s) needed
3. Identify appropriate specimen collection kit(s) needed for the visit
4. Complete serum and urine form for each patient
5. Check tube expiration dates
6. Affix bar coded accession number labels to test tubes and appropriate form(s) and write subject's id and alphacode.

Please note that you will not use all of the barcode labels on each sheet. Please discard all unused barcode labels.

BLOOD COLLECTION

Order of Blood Draw

1. Serum Separator Tubes (SST) (gel barrier) (tiger top)
2. Lavender Top Tubes (EDTA additive)

Serum Blood Draw – (Serum Separator Tube - SST)

1. Using proper technique, collect specimen in the Serum Separator Tube (tiger top)
2. Fill tube(s) completely. Tubes are vacuum tubes and will fill to the correct amount, once the tube top is punctured.
3. Invert tube 5-10 times gently to mix.
4. Label each tube lengthwise with corresponding bar-coded accession label and subject's id and alphacode.
5. Stand tubes upright to allow the specimens to clot at room temperature for 20 to 30 minutes, but no longer than 60 minutes.
6. Centrifuge SST (within 60 minutes of collection) for 15 minutes at 3000rpm, to separate the cells from the serum. Unless indicated, send sample in original tube.
7. Unless otherwise indicated, refrigerate specimen in LifePak™ tray, prior to same day shipment
8. Snap to close LifePak. Secure lid closure by snapping 2 press indicators

Whole Blood Samples (Lavender top tube, EDTA)

1. Using proper technique, collect specimen into Lavender top tube
2. Allow tube to fill completely to ensure proper mix of anticoagulant to blood. Tube is a vacuum and will fill to correct amount once top is punctured
3. Invert 5-10 times gently to mix
4. Label each tube lengthwise with corresponding bar-coded accession label and subject's id and alphacode.
5. Unless otherwise indicated, refrigerate specimen in LifePak™ tray, prior to same day shipment.
6. Snap to close LifePak™. Secure lid closure by snapping 2 press indicators.

URINE COLLECTION

Spot (Random) Urine Collection

1. Have the subject provide a urine specimen in the urine cup (fill cup)
2. Screw the top of the urine cup firmly in place
3. Label urine cup with corresponding bar-coded accession label and subject's id and alphacode.
4. Peel back the label on top of cap to expose the integral sampling device
5. Place yellow conical tube into the sampling device with the rubber stopper facing down. Push down on the tube firmly to pierce the stopper. Urine container should be upright (not tipped) when drawing urine into the tube to prevent air from being sucked into tube
6. Hold the tube until urine stops flowing into the tube
7. Discard the cup as a contaminated sharp
8. Place the urine tube into the LifePak™ tray and keep refrigerated until shipping

24-Hour Urine Collection – (See next page for measuring urine collections greater than 4,000 mL)

1. Measure the approximate volume of the urine based on the jug lines
2. Weigh the urine collection (includes the urine, jug with lid and the preservative)
3. Thoroughly mix the urine collection container
4. Unscrew the top of a urine cup
5. Pour about 50mL of urine from the jug into the cup
6. Screw the top of the urine cup firmly in place
7. Label urine cup with corresponding bar-coded accession label and subject's ID and Alphacode.
8. Peel back the label on top of cap to expose the integral sampling device
9. Place yellow conical tube into the sampling device with the rubber stopper facing down. Push down on the tube firmly to pierce the stopper
10. Hold the tube until urine stops flowing into the tube
11. Discard the cup as a contaminated sharp.
12. Place the urine tube into the LifePak™ tray and keep refrigerated until shipping



If it is necessary to hold specimens overnight before shipping, be sure to place them in a refrigerator.

Processing 24-hr Urine Specimens Greater Than 4,000 mL:

1. Add approximate volume of jug 1 and the approximate volume of jug 2 using jug lines and enter on Form 335.
2. Pour contents of both urine collection containers into an appropriate volumetric flask and mix well.
3. Record this total volume in the weight field on Mailing Form 335.
4. Fill the urine collection cup using the method of your choice (pour, pipette)
5. Continue on using the *24-Hour Urine Collection* instructions on previous page.

Sample Barcode Labels – see next page.

**DO NOT SEND FGF23 materials to SPECTRA – See Chapter 55
on FGF23 processing and shipping.**

Sample Barcode Labels

(Be sure that there are two sheets of barcodes when opening the kit from Spectra.)

Sample Only – Use One Sheet for Form 331-Spectra Serum/Blood/Spot Urine Mailing Form

<p>Use this label on SST tiger top serum tube</p>	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 2px;"> <p style="font-size: 8px; margin: 0;">SST GEL</p> <p style="font-size: 10px; margin: 0;">13000000Q</p> <p style="font-size: 8px; margin: 0;">PT.</p> </td> <td style="width: 50%; padding: 2px;"> <p style="font-size: 8px; margin: 0;">REQUISITION</p> <p style="font-size: 10px; margin: 0;">000000Q</p> <p style="font-size: 8px; margin: 0;">PT.</p> </td> </tr> <tr> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">GOLD POST</p> <p style="font-size: 10px; margin: 0;">23000000Q</p> <p style="font-size: 8px; margin: 0;">PT.</p> </td> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">LAVENDER</p> <p style="font-size: 10px; margin: 0;">12000000Q</p> <p style="font-size: 8px; margin: 0;">PT.</p> </td> </tr> <tr> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">URINE CHEMISTRIES</p> <p style="font-size: 10px; margin: 0;">54000000Q</p> <p style="font-size: 8px; margin: 0;">PT.</p> </td> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">LIGHT BLUE / COAG</p> <p style="font-size: 10px; margin: 0;">15000000Q</p> <p style="font-size: 8px; margin: 0;">PT.</p> </td> </tr> <tr> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">UPANALYSIS</p> <p style="font-size: 10px; margin: 0;">36000000Q</p> <p style="font-size: 8px; margin: 0;">PT.</p> </td> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">MISCELLANEOUS</p> <p style="font-size: 10px; margin: 0;">11000000Q</p> <p style="font-size: 8px; margin: 0;">PT.</p> </td> </tr> <tr> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">MISCELLANEOUS</p> <p style="font-size: 10px; margin: 0;">11000000Q</p> <p style="font-size: 8px; margin: 0;">PT.</p> </td> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">MISCELLANEOUS</p> <p style="font-size: 10px; margin: 0;">11000000Q</p> <p style="font-size: 8px; margin: 0;">PT.</p> </td> </tr> <tr> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">000000Q</p> <p style="font-size: 8px; margin: 0;">SITE USE ONLY</p> </td> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">000000Q</p> <p style="font-size: 8px; margin: 0;">SITE USE ONLY</p> </td> </tr> <tr> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">000000Q</p> <p style="font-size: 8px; margin: 0;">SITE USE ONLY</p> </td> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">000000Q</p> <p style="font-size: 8px; margin: 0;">SITE USE ONLY</p> </td> </tr> <tr> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">Urine Vol.: _____</p> </td> <td style="padding: 2px;"> <p style="font-size: 8px; margin: 0;">Pt. 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		<p>Use this label on EDTA Lavender top tube #1</p>																				
<p>Use this label on yellow conical tube for the spot urine</p>																						
		<p>Use this label on EDTA Lavender top tube #2, if visit requires</p>																				

Sample Only – Use Other Sheet for Form 335-Spectra 24hr Urine Mailing Form

SST GEL 1351440SQ	REQUISITION 51440SQ
GOLD POST 2351440SQ	LAVENDER 1251440SQ
URINE CHEMISTRIES 5451440SQ	LIGHT BLUE / COAG 1551440SQ
URINALYSIS 3851440SQ	MISCELLANEOUS 1151440SQ
MISCELLANEOUS 1151440SQ	MISCELLANEOUS 1151440SQ
51440SQ SITE USE ONLY	51440SQ SITE USE ONLY
51440SQ SITE USE ONLY	51440SQ SITE USE ONLY
Urine Vol.: _____	Pt. Ht.: _____
Total Hrs.: _____	Pt. Wt.: _____

Use this label on Form 331-Mailing

Use this label on yellow conical tube for 24-hr urine

PLEASE USE PATIENT DATA STICKERS ABOVE!
 Catalog No. 88-3333-7 (6/2010) 21 120697-07
 **Rockleigh, NJ 07647**

**GOOD SAMPLE PREPARATION MEANS ACCURATE RESULTS
USE THE INSIST METHOD**



INVERT.....gently, DO NOT SHAKE
NOTE any special handling instructions
STANDSST to clot at least 30 minutes no more than 60 minutes
INSPECT..... tubes before centrifuging to assure a clot has formed
SPIN.....centrifuge SST for 15 minutes
TRANSPORT.....refrigerate/freeze sample as required. Follow shipping instructions



UNSPUN – clotted blood remains on top of gel barrier. Spin specimen in centrifuge for at least 15 minutes (this should be done no longer than 1 hour after drawing the specimen).



INCOMPLETE SEPARATION- serum is not completely separated from the red cells. Centrifuge again for 10-15 minutes. Cells left in serum can affect certain results.



HEMOLIZED SPECIMEN- serum is red or pinkish. If possible redraw specimen. Cells left in serum can affect certain results.

INSIST on quality specimens for quality results

Invert- shaking the specimen can cause hemolysis

Note- special instructions, i.e. freezing

Stand- specimen must be clotted before spinning to achieve good separation

Inspect- make sure the specimen has clotted

Spin- centrifuge specimen for 15 minutes at 3000rpms for good separation,
if necessary re-spin

Transport- follow instructions from Spectra lab

Packaging and Shipment of Safety Laboratory Specimens to Spectra

DO NOT SEND FGF23 materials to SPECTRA – See Chapter 55 on FGF23 processing

1. Make sure Federal Express has been called to schedule pick up or use regular pick-up service
2. Place tubes in specimen trays (refer to Tray Packaging System) such as LifePak that says ‘Spectra Laboratories’ embossed on it?
3. Place tray in small zip lock bag
4. Place the zip lock bag into RESEARCH Biohazard SAFETY BAG along with a completed serum and urine mailing form(s)
5. Seal bag
6. Place bag in preprinted Spectra Shipping box
7. Fold box divider over and place ice pack in box
8. Close the box and seal with tape
9. Complete airbill addressed to SPECTRA* by filling in box # 1 with your site information including site number and phone number
10. Affix airbill addressed to SPECTRA to box
11. Make sure airbill is marked **PRIORITY OVERNIGHT**
12. Mark weight in box #6 as <2lbs, with no declared value

Complete the top portion of the air bill.

If shipping on Friday be sure to check the Saturday Delivery box **AND** Use a Saturday Delivery label

The image shows a FedEx USA Airbill form. Key sections include:

- 1 From:** Sender's name, address, and phone number.
- 2 Your Internal Billing Reference:** 3800
- 3 To:** Recipient's name, address, and phone number.
- 4a Express Package Service:** Includes checkboxes for Priority Overnight, Standard Overnight, and First Overnight.
- 4b Express Freight Service:** Includes checkboxes for 1Day Freight, 2Day Freight, and 3Day Freight.
- 6 Special Handling:** Includes checkboxes for Saturday Delivery, Sunday Delivery, and Hold Saturday.
- 7 Payment:** Includes checkboxes for Sender, Recipient, Third Party, Credit Card, and Cash/Check.
- 8 Release Signature:** A line for the sender's signature.

Handwritten information includes tracking number 8156 6052 6537, weight 021.5, and recipient address: SPECTRA EAST, B KING RD, ROCKLEIGH, NJ 07647-2502.



Packaging



Customer Service
(800) 517-7157 ext 5330

Tray Packaging System

Small Tray Shipper

1. Assemble shipping box.



2. Place tubes into tray(s).



3. Place up to 4 trays and ALL paperwork into the clear poly bag and seal the bag.



4. Place the sealed bag in the box.



5. Fold over cardboard separator, and place 1 ice pack on top.



6. Seal box with tape and affix airbill to box.



Shipping - General Information

Ideally, Spectra samples should be shipped the same day they are collected. If not, the sample should be stored in the refrigerator until the next day when it can be shipped.

Sites can ship to Spectra Monday-Friday but Monday-Thurs is best. If shipping on Friday for a Saturday delivery, mark Saturday delivery on the packing slip and also place a sticker on the box that says "Saturday delivery". Sites can also ship on Saturday, but need to ship from FedEx depot (not a Kinkos- they won't take packages with UN3373 number on box).

Blood must be received at Spectra within 4 days of the draw date for the sample to be processed.

Reporting - General Information

Reference Ranges

Most reference ranges for tests performed at Spectra are those reported by the manufacturer of the assay reagents for the particular methodology used. For ranges that vary by gender or age, the applicable range will be indicated based on the patient demographic information provided to Spectra. Values outside the reference range will be automatically flagged as High or Low.

Alert Values

Alert values require immediate attention and are returned to the site via fax as soon as they are available in the laboratory. A follow-up telephone call is made to confirm receipt of the fax.

Reports

Spectra Reports are returned to the site via fax. These reports will not include calculations (eg. eGFR or 24-hour clearances.)

Reports will also come from the DCC containing any calculations required and other information as applicable.

Turn-Around-Time

Routine chemistry and hematology tests are performed within 24 hours of Spectra's receipt of a specimen. If you have any questions regarding reports or failed transmission please call any member of your Spectra team. Note, that Spectra is not a STAT lab. It is conceivable, that if a sample is collected on a Thursday and shipped on Thursday, Spectra will receive the sample on Friday but may not analyze it until Monday and results sent to the site on Tuesday.

Test Cancellation

Tests will be cancelled by Spectra when specimens are received in a condition that does not allow accurate testing. These include the following:

Unspun: Uncentrifuged serum samples are only suitable for BUN, Creatinine, Albumin and Serology testing. All other tests will be cancelled. The listed tests will only be performed if, after centrifuging the specimen, it is found to not be hemolyzed.

Gross Hemolysis: Glucose, Electrolytes and Enzymes are affected by gross hemolysis and will not be performed.

Moderate hemolysis: Specimens received in this condition will be tested and the results reviewed. In many cases the results will be reported with a comment indicating the specimen condition.

Clotted, Hemolyzed or Grossly under filled: Hematology tests (CBC) will be cancelled on specimens with these conditions.

Sites and the DCC will be notified of test cancellations and the corresponding mailing form will be flagged.

COMBINE STUDY

Appendix 1-Adding Acid to Urine Containers

24-Hour Urine Collection

- Spectra urine jugs must contain a preservative in order for the participant to accurately complete a 24-hour collection. Each jug must contain 30 ml of 6N hydrochloric (HCl) acid preservative.
- Each COMBINE site must add the 6N HCl acid to each jug prior to giving the urine collection jug to a participant.

Items to have on hand before attempting to add the acid to the jug:

- 1 (or 2)-4L Urine collection container(s) (jug) with lid
- 6N Hydrochloric Acid
- Other required equipment as designated by your institution's guidelines
- Fumes warning stickers for urine jug (sent by DCC to each site)



Procedure:

- Allow adequate time to complete process.
- Remove lid from jug and set aside.
- Pour exactly 30 ml of 6N HCl acid into the jug following your institution's guidelines.
- Place lid on opening and tighten lid down.
- Check for any HCL spillage on outside of urine container and follow your institution's guidelines for how to clean up any spillage.
- Add fumes warning sticker to the jug.

Spectra Critical Lab Values for COMBINE Randomized Participants

Phosphorus:

Critical low value: < 2.8 mg/dl

Critical high value: \geq 5.9 mg/dl

Platelet:

Critical low value: < 100,000/mc

AST (SGOT):

Critical high value: > 160 U/L

ALT (SGPT):

Critical high value: > 180 U/L

Total Bilirubin:

Critical high value: > 4.8 mg/dl

Alkaline Phosphatase:

Critical high value: > 520 U/L

Creatine Kinase:

Critical high value: > 800 U/L



COMBINE

STUDY COORDINATOR: _____

SITE NO: _____

PHONE: _____

DATE: _____

Shipping Address: _____

ITEM	UNITS	QUANTITY
Kit 3494	EACH	
Kit 3495	EACH	
Kit 3496	EACH	
Kit 3497	EACH	
24 Hr. HCL Urine Jug	EACH	
Airbills	25 EACH	

PLEASE FAX SUPPLY RE-ORDER SHEET TO **201-767-7358**, ATTENTION:

Richard Merwede

PLEASE ALLOW 10 BUSINESS DAYS FOR DELIVERY

IF YOU HAVE ANY QUESTIONS OR NEED FASTER DELIVERY, PLEASE CONTACT US @ 800-517-7157 EXT 5330

Participant 24-Hour Urine Collection Instructions - COMBINE

1. Start the 24-hour urine collection on the morning before your study visit.
2. On the collection day, **do not** save the first morning urine you pass. Record the date: _____ and time: _____ of this first urine.
3. Collect **ALL** your urine day and night for the next 24 hours.
4. Your last urine collection should be exactly 24 hours after the time recorded above in # 2.

Example:

- **Thursday morning at 7:00 am:** Empty your bladder into the toilet. **DO NOT** save the urine. Record 7:00 am on the collection bottle.
- After the first urine, save **ALL** urine voided (day and night).
- **Friday morning at 7:00 am:** Empty your bladder and **SAVE** this urine. This is the last collection that you need to save. Record the exact time on the collection bottle.

Additional Notes:

- ❖ **CAUTION:** The collection bottle contains an acid preservative. AVOID splashing or spilling this liquid when pouring urine into this container. (Note: This container will have a terrible odor once urine is added to it.)
 - *If you are splashed by ACID:
 - EYES immediately begin flushing with water and continue for 15 minutes. Notify your Doctor right away.
 - SKIN, Immediately wash with cold water and notify the study physician if a rash, swelling or pain develop.
- ❖ Keep the urine collection in a cool area (a basement is fine if you'd rather not use the refrigerator).

Hydrochloric Acid Information Sheet that Site 32 (Denver Nephrology) gives to COMBINE participants prior to collecting the 24-hour urine

The urine collection container will have a chemical called hydrochloric acid inside to preserve the substance to be tested. The name of the chemical will be on the container. Because there is some hazard associated with these chemicals, keep the container out of the reach of children. The risk of injury from the chemical decreases as the container becomes filled with urine.

Hydrochloric acid can irritate your skin and could be harmful to your eye. If swallowed, it could damage your esophagus or stomach. If you breathe in dust or fumes, they could be harmful to your lungs. Hydrochloric acid can also be absorbed through your skin.

Actions: If you or another member of your family should accidentally come in contact with the preservative, take the following actions:

- If you spill the hydrochloric acid, wear rubber gloves and cover the spill with baking soda. Mix until there is no more bubbling, then mop up with water and discard down the drain. If baking soda is not available, mop up with water and then rinse the area thoroughly with water. Run water for five minutes after discarding down the drain.
- If you get any chemical on your skin, rinse well with tap water to remove it. Remove any contaminated clothing and rinse well with water. **DO NOT** add baking soda to hydrochloric acid on the skin or in the eye.
- If you splash chemical into your eye, rinse the eye with cool tap water for 15 minutes. Try to hold the upper and lower eyelid open while rinsing. Have the eye checked by a physician.
- If you breathe in dust or fumes, move to an area with fresh air. If breathing is difficult, seek medical attention.
- If a family member swallows any chemical, take the following actions and seek medical attention immediately:
 - **Hydrochloric Acid: DO NOT** induce vomiting. If the victim is conscious, give 2-4 cupfuls of milk or water.

You will receive a written set of instructions outlining how to safely collect the 24 hour urine specimen. You will also be provided latex containing medical gloves to wear in the event of a spill of the hydrochloric acid or while transferring urine into the collection container.

COMBINE FGF23 and R01 Kit

Procedure Manual (Draft)

Clinical Research Laboratory Study Coordinator
Kim van Leuven, MT(ASCP)
kvanleu@u.washington.edu
(206) 543-9032

Laboratory Director
Andrew N. Hoofnagle, MD PhD
ahoof@u.washington.edu
(206) 598-6131

1. General Information

Timing of Blood Draws

Serum and plasma samples will be drawn for FGF23 and other biomarkers (R01) on the following study visits: B1, B2/F0, F1, F2, F3, F6, F9, and F12.

Specimens will be processed as described below and stored frozen at -80 to -70°C until they are ready to be shipped to the University of Washington. Specimens will be shipped on dry ice monthly.

Blood Draw Supplies

Supplies for the actual blood draw and aliquotting for the COMBINE Study, including the **FGF23 and R01 kit**, will be provided by Spectra Laboratories. All start up supplies will be sent to your site prior to the start of this clinical trial. The FGF23 study kit will be placed in a separate plastic bag. Please be aware of the expiration date of the test tubes and do not use them past the expiration date.

Should you need additional FGF23 kits at any point during this clinical trial, you can order more supplies using the reorder sheet provided by Spectra; faxing instructions to order additional supplies from Spectra are denoted on the reorder sheet. Or you may call 1-800-517-7157 Option 2.

Requisition (Form 329)

Please use mailing form 329 for all samples being sent to the University of Washington. These requisitions are available for download from the Data Coordinating Center (<https://qhsapps.ccf.org/ckdp/>). Please complete ALL THE REQUESTED INFORMATION ENTIRELY including the appropriate visit number. Be sure to barcode the requisition with each of the four requisition barcode labels provided and make a copy to send to the University of Washington (keep the original for your records). Enter the information into the Data Coordinating Center Database when the samples are ready for shipment (ideally, each month).

Shipping Supplies

At the start of the study, an FGF23 and R01 Kit Shipping Container will be sent to your site by the University of Washington Laboratory. It will contain two smaller cardboard boxes for aliquots to be stored at -80 to -70°C until shipping. There will also be barcoded labels included in the shipping box for use in preparing the specimens. Also included will be a pre-paid FedEx shipping label. Barcode labels and pre-paid FedEx labels need to be ordered thru UW by sending an email to Kim van Leuven (kvleuven@uw.edu) and Andy Hoofnagle (ahoof@uw.edu). The shipping box will need to be filled with dry ice and sealed with packing tape prior to shipping. ***It is the responsibility of each site to obtain dry ice and packing tape for each shipment.***

Clinical Site Information

Day of Month to Ship to UW

CLINICAL CENTER 11: GEORGE WASHINGTON UNIVERSITY	Days 1 to 5
CLINICAL CENTER 21: NORTHWESTERN UNIVERSITY SCHOOL OF MEDICINE	Days 6 to 10
CLINICAL CENTER 22: NORTHSHORE UNIVERSITY HEALTH SYSTEM (COMBINE only)	Days 11 to 15
CLINICAL CENTER 31: UNIVERSITY OF CALIFORNIA SAN DIEGO	Days 16 to 20
CLINICAL CENTER 32: DENVER NEPHROLOGY	Days 21 to 25
CLINICAL CENTER 41: UNIVERSITY OF UTAH	Days 26 to 30

COMBINE FGF23 Kit Procedure Manual

FGF23 Blood Collection Kit

Combine FGF and R01 kit contents		
Catalog number	Description	Number Included
88-3470-2	Cryovial, 2mL	4
88-3026-6	8.5mL Serum Separator Tube	1
	4mL Lavender top	1
	Pipettes	2
87-0252-4	Clear Bag, Small	1

2. Shipping box contents

Provided by the University of Washington Laboratory

FGF23 and R01 Kit Shipping Container (first container sent to each site)		
Catalog number	Description	Number Included
NA	Set of barcoded sample labels <i>Each set of labels will have four pairs of barcoded labels. One label from each pair is for a cryovial, the other label from each pair is for the requisition form</i>	12
11-678-24A	Revco cryovial storage box	2
S-12682	ULine dry ice shipping box 12x12x9	1
NA	Preprinted FedEx shipping label**	1
NA	Dry Ice Shipping label	1

The first shipping container will contain two Revco boxes. After the first Revco box is sent back to the University of Washington, please use the second box to store FGF23 plasma and serum samples prior to sending the next shipment. Ideally, each site will have at least one COMBINE FGF23-labeled Revco box onsite at all times.

FGF23 and R01 Kit Shipping Container (subsequent containers)		
Catalog number	Description	Number Included
NA	Set of barcoded sample labels <i>Each set of labels will have four pairs of barcoded labels. One label from each pair is for a cryovial, the other label from each pair is for the requisition form</i>	6 to 12
11-678-24A	Revco cryovial storage box	1
S-12682	U-Line dry ice shipping box 12x12x9	1
NA	Prepaid FedEx shipping label**	1
NA	Dry Ice Shipping label	1

3. Blood Draw and sample processing

Procedure for blood draw and making aliquots

1. Obtain the appropriate blood draw kit for the visit number (kits provided by Spectra)
2. Obtain an FGF23 and R01 blood draw kit (COMBINE FGF and R01 kit, provided by Spectra)
3. Print one Form 329 from the Data Coordinating Center website: (<https://qhsapps.ccf.org/ckdp/>)
4. Label the four 2mL cryovials from the FGF23 and R01 blood draw kit: two of the cryovials should have “serum” barcode labels and two of the cryovials should have “plasma” barcode labels. Place one of each of the four barcode labels on the requisition (Form 329). Write the Subject ID on the tube with Sharpie marker.



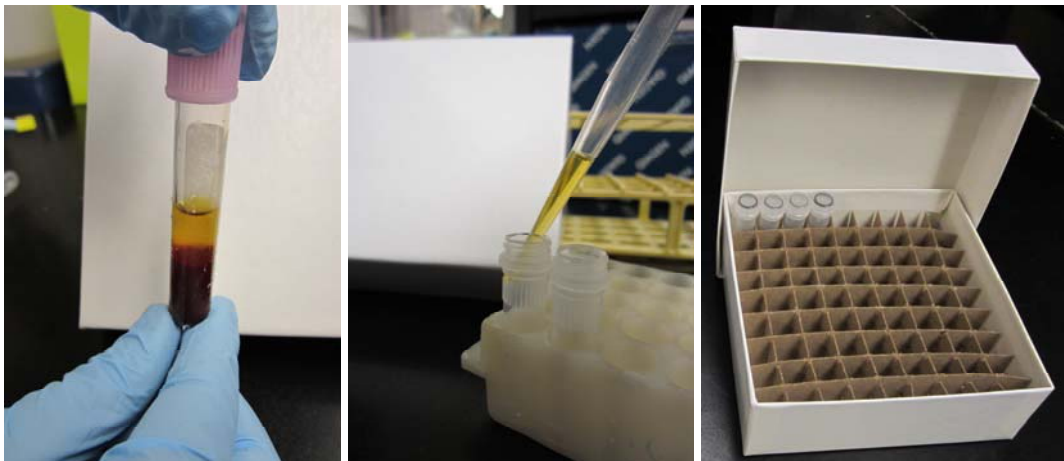
Note the orientation of the barcode along the vertical axis of the cryovial.

5. Draw the serum separator tubes (SST) and then the EDTA whole blood tubes for the safety labs and FGF23 and R01 in the proper order (serum first, plasma second)

Refer to the Spectra Laboratory Services Manual for proper blood draw technique.

6. Centrifuge the EDTA plasma tube for 15 min at 3000 rpm
7. Using a pipet, transfer approximately half of the plasma (regardless of the volume) to one of the labeled cryovials (be sure to use a cryovial labeled PLASMA)
8. Using the same pipet, transfer the remaining plasma to the second cryovial labeled PLASMA, being sure not to disturb the cells at the bottom of the tube

If the cell layer is disturbed, recentrifuge for 5 min at 3000 rpm and remove the remaining plasma. Please note on the Form 329 if the sample was recentrifuged.



COMBINE FGF23 Kit Procedure Manual

9. Immediately place the FGF23 and R01 plasma samples in the Revco sample storage box and place in the deep freezer (-80 to -70°C)
10. Allow the serum to continue to clot upright at room temperature for a total of 20-60 min
11. Centrifuge the serum separator tubes for 15 min at 3000 rpm
12. Using a clean pipet, transfer approximately half of the serum to one of the labeled cryovials (be sure to use a cryovial labeled SERUM)
13. Using the same pipet, transfer the remaining serum above the gel to the second cryovial labeled SERUM
14. Immediately place the FGF23 and R01 serum samples in the Revco sample storage box and replace in the deep freezer

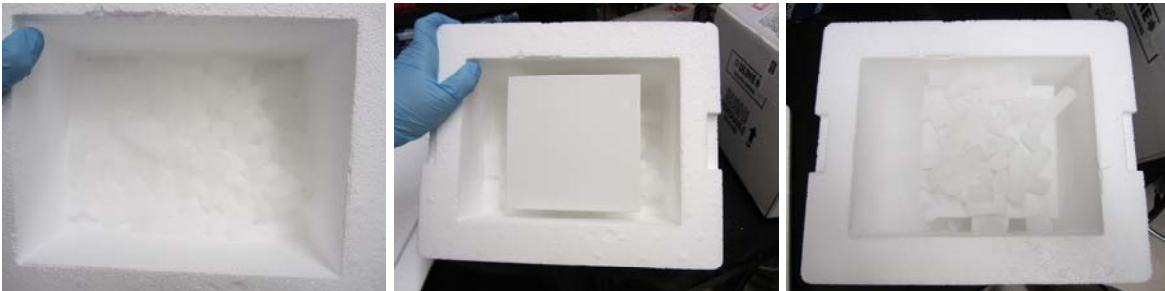
You will use the same Revco sample storage box for FGF23 and R01 serum and FGF23 and R01 plasma storage for the next subject

15. Fill out the Requisition (Form 329) in its entirety for each subject drawn

4. Sample Shipment

Preparing the samples for shipment to the UW Laboratory

1. Contact FedEx to arrange for pickup (must be sent Monday-Wednesday)
2. Print out the shipping form from the Data Coordinating Center website: (<https://qhsapps.ccf.org/ckdp/>) and fill it out completely.
3. Partially fill the U-Line shipping container with dry ice
4. Place the Revco box of samples into shipping container
5. Add dry ice until the container is at least $\frac{3}{4}$ full with dry ice



6. Place the Styrofoam lid on top of the Styrofoam box
7. Place the Requisitions (Form 329) on top of the Styrofoam lid
8. Also place the Shipping forms (Form 330) on top of the Styrofoam lid

Please be sure to make a copy of the barcoded Requisitions (Form 329) to include with each shipment and keep the originals for your records.

9. Close the lid of the cardboard box and secure with packing tape
10. Place the prepaid label in the FedEx shipping sleeve and attach to the cardboard box
11. Affix a Dry Ice Label to the outside of the cardboard box



COMBINE FGF23 Kit Procedure Manual

12. The package is ready to be picked up by FedEx
13. Email the tracking number to:
 kvueven@u.washington.edu
 ahoo@u.washington.edu

Pilot Clinical Trials in CKD
MANUAL OF OPERATIONS
COMBINE Study
Cardiac and Renal MRI Chapter

Northwestern University 4D Lab
NorthShore Lab

CONTENTS

1. Overview	2
2. Pilot Clinical Trials in CKD MRI Steering Committee	3
3. MRI Core Laboratory	4
a. Personnel	4
4. Site Preparation and MRI Validation	5
a. Certification of Local Clinical Center Staff	6
b. Site Validation	6
Both studies acceptable:	7
One or both studies unacceptable	7
Figure 1. Site Preparation and Validation for Cardiac & Renal MRI	8
5. Image Acquisition Protocol: COMBINE study – Cardiac & Renal MRI	9
a. MRI Equipment & Hardware	9
b. Patient Identification on Recorded Images – Patient Confidentiality	9
6. Data Transfer and Management	10
a. Clinical Center Workflow	10
b. Electronic Data Transfer Instructions	10
c. Data Transfer via Mail	10
d. Data report from the DCC	10
7. Image Quality Review	10
a. Incomplete and Un-interpretable Cardiac Image-sets:	11
b. Incomplete and Un-interpretable Renal Image-sets:	11
8. Image Analysis	12
a. Methods	12
9. Reporting of Image Analysis Results	13
10. Quality Assurance and Quality Control of Image Acquisition	14
a. MRI Qualification of sites and Quality Assurance for Image Acquisition	14
b. MRI Core Lab Review of Images	14
11. Cardiac & Renal MRI Training and Additional Site Support	14
11. Appendices	16
i. Image Acquisition Protocol	17
a. Cardiac Participant Preparation	17
b. Renal Participant Preparation	17
c. Image Acquisition	17
ii. Instructions for COMBINE Study Cardiac Imaging (Cine series)	19
iii. Instructions for COMBINE Study Cardiac Flow Imaging (Phase Contrast)	21
iv. Instructions for COMBINE Study Renal Imaging	22
v. COMBINE Study Cardiac Sequence Parameters	24
vi. COMBINE Study Renal Sequence Parameters	27
vii. Data Transfer Instructions	30

1. Overview

The COMBINE (CKD Optimal Management with Binders and NicotinamidE) Study is a multi-center clinical trial being carried out by the NIDDK-funded Pilot Clinical Trials in CKD Consortium. Eligible participants will be enrolled at seven clinical centers (#11 George Washington University; #21 Northwestern University; #22 NorthShore University Health System; #31 University of California San Diego; #32 Denver Nephrology; #41 University of Utah, and #43 University of Utah VA. The Data Coordinating Center (DCC) for the CKD Consortium is at the Department of Quantitative Health Sciences at the Cleveland Clinic.

The COMBINE study is a 12-months, randomized, double-blinded, four arm parallel study in 200 CKD stage 3–4 patients (50 in each of the four treatment groups) investigating the effects of the interventions on changes in serum phosphate and FGF23 levels. Participants will be randomized to one of the four groups: 1) lanthanum carbonate + nicotinamide; 2) lanthanum carbonate + nicotinamide placebo; 3) lanthanum carbonate placebo + nicotinamide; 4) lanthanum carbonate placebo + nicotinamide placebo.

The main study will test the following hypotheses:

1. Compared to placebo, monotherapy with nicotinamide, monotherapy with lanthanum carbonate, and combined nicotinamide and lanthanum carbonate therapy will lower serum phosphate and FGF23 levels.
2. Combined treatment with nicotinamide and lanthanum carbonate will be safe, well-tolerated, and acceptable to CKD participants, demonstrating feasibility of long-term compliance in a subsequent phase 3 clinical trial.

The following hypotheses will be tested in the Magnetic Resonance Imaging (MRI) component of the study:

1. Compared with placebo, active therapy with nicotinamide and lanthanum carbonate will reduce or blunt the increase in LV mass index; attenuate LV diastolic dysfunction, indicated by increased LV end diastolic volume and decreased left atrial volume (all measures assessed by gadolinium-free Cardiac MRI).
2. Compared with placebo, active therapy with nicotinamide and lanthanum carbonate will improve intra-renal oxygenation and stabilize or reduce progression of renal fibrosis, as assessed by gadolinium-free renal BOLD and Diffusion MRI.

We anticipate sufficient power for secondary outcome number 1, change in LV Mass Index. The other analyses should be considered exploratory. The outcome variables based on MRI are listed in Section 9.

1. *Change in LV mass index [Cardiac MRI]*
2. *Change diastolic dysfunction as measured by Left Ventricle (LV) end diastolic volume [Cardiac MRI]*
3. *Change diastolic dysfunction as measured by Left Atrial (LA) end-diastolic (ED) and end-systolic (ES) volume [Cardiac MRI]*
4. *Change in renal fibrosis as measured by apparent diffusion coefficient (ADC) [BOLD Renal MRI]*

5. *Change in intra-renal oxygenation (as measured by change from baseline in pre-furosemide relaxation rate ($R2^*$) in the cortex and medulla) [BOLD Renal MRI]*
6. *Change in intra-renal oxygenation (as measured by change from baseline in post-furosemide relaxation rate ($R2^*$) in the cortex and medulla) [BOLD Renal MRI]*
7. *Change from pre to post-furosemide relaxation rate ($R2^*$) in the cortex and medulla at baseline [BOLD Renal MRI]*
8. *Change from pre to post-furosemide relaxation rate ($R2^*$) in the cortex and medulla at F12 [BOLD Renal MRI]*

The DCC will provide guidance to the investigative team with analyses plans. The PI, Dr. Tamara Isakova, will oversee the primary analyses of the ancillary study's end points at Northwestern University.

COMBINE participants who are willing and able to take part in the MRI components of the study will undergo non-contrast cardiac and renal MRI examinations at Baseline and at the end of study. All imaging studies will take place after informed consent has been obtained from the participants.

The MR image acquisition protocol established by the MRI Steering Committee for the study is provided in the Appendix i.

The clinical centers outside of Northwestern University will send each participant's MRI dataset to the Northwestern University Radiology 4D Lab (henceforth NURAD4D) for image analysis in order to calculate changes in cardiac and renal function from baseline to end of study (e.g., if renal oxygenation improves or worsens). The results of these analyses will then be reported to the Data Coordinating Center (DCC) at Cleveland Clinic.

This MRI Manual of Operations details the roles of the Pilot Clinical Trials in CKD MRI Steering Committee and the MRI Core Laboratories, and the protocols for 1) MRI Technologist Certification, 2) MRI Site Validation, 3) Image Acquisition, 4) Data Transfer and Data Management, 5) Image Quality Review, and 6) Image Analysis.

2. Pilot Clinical Trials in CKD MRI Steering Committee

The Pilot Clinical Trials in CKD MRI Steering Committee (henceforth, CMRSC) determines an MR image acquisition protocol as documented in this Manual of Operations for use in the study. The members of the CMRSC (Tamara Isakova, MD; James Carr, MD; Michael Markl, PhD; Pottumarthi Prasad, PhD; Susanne Schnell, PhD; Maria L. Carr, RT.R (MR)) have considerable expertise in clinical and research MRI and collectively have experience with equipment manufactured by all of the major MRI vendors. The CMRSC will provide the techniques for image acquisition and analysis as they pertain to the COMBINE study.

The CMRSC will offer solutions to technical problems with image acquisition and/or image analysis, as reported by the NURAD4D or NorthShore University HealthSystem (henceforth NorthShore).

The CMRSC will also meet on an ad hoc basis with industrial liaisons from the MRI vendors for

technical input and support, so that assistance can be provided to sites, which require additional guidance for image acquisition.

The CMRSC will provide solutions to the COMBINE study regarding sites, which are persistently underperforming with respect to acquisition of MRI datasets of an acceptable quality.

Furthermore, the CMRSC will advise on the MRI aspects of publications arising from the study, following the publications policies of the Pilot Clinical Trials in CKD Consortium for publication or presentation of findings related to (and scientific papers which focus on) the MR image acquisition and/or analysis technique(s).

If techniques for image acquisition and/or cardiac and renal endpoints change during the course of the trial, the CMRSC may advise alterations to the procedures described in this Manual of Operations.

3. MRI Core Laboratory

The primary function of the COMBINE Study MRI Core Laboratory (henceforth, MRI Core Lab) is to provide measurements of cardiac and renal function for each participant enrolled in this study via analysis of their MRI datasets.

In order to ensure consistency and acceptable image quality, the MRI Core Lab will also be responsible for validating clinical centers by their ability to produce image-data, which is of acceptable quality for use in the study. Furthermore, the MRI Core Lab will employ secure and efficient data transfer and management protocols, and will be responsible for quality assurance and quality control of the MRI data generated in the study.

The consortium's MRI measurements will be transmitted to the Data Coordinating Center (DCC) to be loaded into the consortium's Oracle 11g database. The MRI Core Lab will also capture data locally using a REDCap data base dedicated to the COMBINE study. REDCap (Research Electronic Data Capture) is a secure, web-based application for building and managing online data capture for research studies. Northwestern University is a member of the REDCap consortium.

The MRI Core Lab will work closely with the CMRSC. If and when high-level technical problems with image acquisition arise at the clinical centers, the MRI Core Lab will present a report on the specific nature of the problem to the CMRSC and will implement solutions.

a. Personnel

Northwestern University, Department of Radiology, 4D Lab personnel include Susanne Schnell, (4D Lab Director, Assistant Research Professor), Maria L. Carr (Research Project Manager), IT support staff, Specialized Imaging Physicians and Fellows, specially trained Research Image Analysts and an MR technologist. These personnel will be directly responsible for the COMBINE cardiac MRI analysis.

NorthShore University, Department of Radiology, Center for Advanced Imaging include Pottumarthi Prasad, Ph.D. (Associate Director), Eugene Dunkle (Research Manager), Wei Li, M.D. (Research Scientist) who will be directly responsible for the COMBINE renal MRI data

analysis. The center includes other experienced physicians, physicists and staff with extensive experience with MRI acquisitions and analysis and will provide input on a need basis. The address directory for both labs can be found at:

http://qhsapps.ccf.org/ckdp/open_webdocs/AddressDirectory/CKDAddressDirectory.pdf

4. Site Preparation and MRI Validation

Each clinical site must consistently acquire cardiac and renal MR image-sets that are complete and of acceptable quality to be used in the study.

The MR image-acquisition protocol and instructions recommended by the CMRSC are included in this section of the Manual of Operations (Appendices ii-iv for instructions, Appendix i for Image Acquisition Protocol). The instructions for data transfer of the MRI studies to the MRI Core Lab can be found in Appendix vii, Data Transfer Instructions

Not all COMBINE Clinical Centers will perform MRIs on site. Clinical Center #32 Denver Nephrology will have MRIs done at the University of Denver; and Clinical Center #43 University of Utah VA will have MRIs done at the University of Utah.

Thus, there will be six COMBINE MRI Sites:

- George Washington University
- Northwestern University
- NorthShore
- University of California San Diego
- University of Colorado at Denver
- University of Utah

Each COMBINE MRI site will name a lead COMBINE MRI Investigator, a radiologist/physicist who will provide oversight for image acquisition to ensure that an image-set, which is complete and acceptable, is obtained for each COMBINE participant who consents to MRI. (See guidelines for image acquisition in appendix v-vi.)

Technical support at each MRI site will be provided by NURAD4D or NorthShore. In addition, each site will be encouraged to work closely with their Lead COMBINE MRI Investigator and MRI radiographer personnel, who will help to address technical issues, system and/or software upgrades, etc. The MRI site personnel will receive directives from the MRI Core Lab and will report any hardware or software updates to the MRI Core Lab. Industrial Liaisons (Siemens) and the MRI Core Lab personnel will meet on an *ad hoc* basis with the CMRSC to address any technical support questions.

Figure 1 shows the process of Site Preparation and Qualification for MRI. The validation of the cardiac portion of the MRI acquisition will be performed at NURAD4D. The renal portion of the analysis will be performed at NorthShore, who will inform NURAD4D of successful site validation. In case the study is not accepted, NorthShore and NURAD4D will communicate this with the imaging site separately via email/phone. The DCC and NorthShore will be copied in this communication.

a. Certification of Local Clinical Center Staff

Before a site MRI technologist can perform a COMBINE study MRI, he/she must first become certified by the MRI Core Lab. It is recommended that at least two technologists per clinical site need to become qualified. The purpose of certification is to ensure consistency and accuracy on how the MRIs are performed study-wide and to ensure highest quality MRIs.

The criteria for determining whether a MRI technologist has met study certification requirements are as follows:

- The MRI technologist must be on a COMBINE MRI Training Call with renal and cardiac MRI core lab staff members. These training calls will include a prepared MS PowerPoint presentation to be shared via screen sharing.

When an MRI technologist has been certified, the COMBINE MRI Core lab will send an email to the site and to the DCC to notify them that the technologist is certified.

b. Site Validation

Prior to enrolling a study participant, each of the four COMBINE MRI Sites outside of Chicago (i.e., George Washington University, University of California San Diego, University of Colorado at Denver, and the University of Utah) must send two test (Healthy Volunteer) cases **de-identified** to the Northwestern MRI Core Lab for validation and assessment. This is also part of the above mentioned local staff certification. The subject study numbers for test data should include the study name and **clinical site number** along with **T001, T002**, etc. For example, **COMBINE Study 21_T001**. These studies must be accompanied by a completed MRI Submission form 291.

http://ghsapps.ccf.org/ckdp/open_webdocs/Forms/Form291.pdf

The MRI Core Lab will email the site to confirm receipt of the two image-sets. The two image-sets, sent by the clinical center for validation, are reviewed at NURAD4D and NorthShore for image quality.

The criteria for determining whether a COMBINE MRI Site is qualified are as follows:

- Two test MRI cases must be supplied by the participating MRI site. Each test case must be de-identified and must i) be complete, and ii) have sufficient resolution and image quality for diagnosis, and iii) have little to no artifact.

Acceptable image quality will be defined as follows:

- All required views should be obtained in a manner consistent with instructions contained within this chapter of the Manual of Operations
- Site should demonstrate the ability to follow directions when sending material to the MRI Core Lab. This includes ensuring that the materials sent to the lab were de-identified.

It is recommended that the two test MRI cases be done by two different COMBINE MRI technologists.

Both studies acceptable:

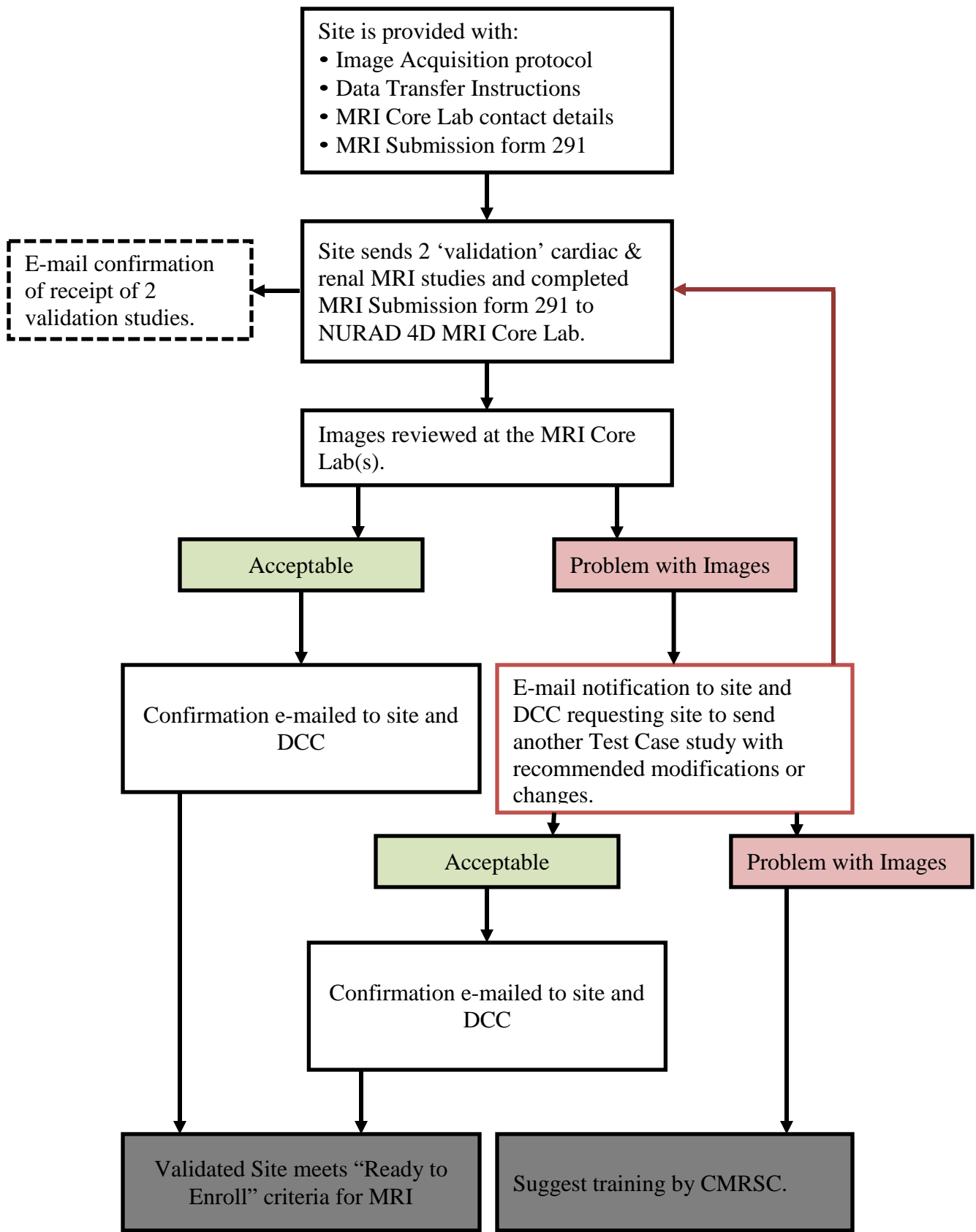
If both of the validation studies are found to be acceptable, an email will be sent to the site and to the DCC to notify them that the site has qualified. On receipt of this confirmation email and if both local MRI technologists are certified, the site will have met the MRI component of the COMBINE Study's "Ready to Enroll" criteria. If all other criteria have been met, the site can formally start performing scans and sending image-sets to the MRI Core Lab for analysis.

One or both studies unacceptable

If one or both of the validation studies are found to be unacceptable, the site and the DCC will be notified by email. This email notification will give the reasons why the study/studies is/are unacceptable, will recommend possible modifications to be made for acquiring acceptable image-sets, and will request that another image-set, acquired with the recommended modifications, be submitted to the MRI Core Lab for validation. The site is requested to send this additional study with another MRI submission form 291.

If this additional study is found to be acceptable, the site and DCC will receive confirmation via email. However, if the additional study is also found to be unacceptable, the site and the DCC will be notified by email. This email notification will describe why the additional MRI study was unacceptable, and will recommend that special training on cardiac or renal MRI be provided to the site to enable them to qualify and therefore participate in the study. The MRI Core Lab is able to coordinate special training for clinical centers which are less experienced with cardiac or renal MRI and had difficulty qualifying for the study based on the validation MRI studies submitted (see Section 11 on Cardiac & Renal MRI Training).

Figure 1. Site Preparation and Validation for Cardiac & Renal MRI



5. Image Acquisition Protocol: COMBINE study – Cardiac & Renal MRI

Enrolling centers are provided with the image acquisition protocol (Appendix i. Image Acquisition Protocol) recommended by the CMRSC to provide acceptable cardiac and renal image quality for the COMBINE study.

The CMRSC has developed a consensus MRI protocol in order to ensure uniform, acceptable and reproducible image quality across the Siemens platforms.

The imaging protocol consists of a series of cine images acquired in the short-axis plane from the Atria of the Left Atrium to the apex of the left ventricle, using the Steady State Free Precession (SSFP) technique. Long-axis SSFP cine series should be acquired in the four-chamber view, the two chamber view and the left ventricular outflow tract. In addition, two 2D flow phase-contrast MRI scans will be acquired in horizontal long axis view and through-plane at the position of the mitral valve. The cine series is followed by renal imaging.

The renal imaging consists of coronal BOLD and Diffusion MR images. BOLD MRI acquisitions are based on breath-hold multiple gradient echo sequence and Diffusion MRI is based on spin-echo EPI under free breathing. BOLD MRI data will be acquired both pre- and post-Furosemide injection at the clinical sites that are participating in the Furosemide section.

Steps for Image Acquisition and the MR sequence parameters for the protocol are given in (Appendices v-vi).

a. MRI Equipment & Hardware

- Siemens 1.5 T Avanto and 3.0 T Siemens Verio and Skyra imaging systems with cardiac pulse sequence package and renal BOLD and Diffusion.
- Minimal requirement: Slew rate: > 150 T/m/sec, maximum gradient strength: > 35 mT/m.
- Dedicated cardiac and body phase-array surface receiver coil of at least 4, and preferably 8, elements.
- Dedicated cardiac gating system. For example, MEDRAD/Invivo, vector ECG gating, etc. Pulse oximetry gating is not preferred due to potential image blurring.

b. Patient Identification on Recorded Images – Patient Confidentiality

- The MRI sites have to ensure to only transfer MRI data to NURAD4D containing no patient identifiers, such as name, date of birth or medical record number.
- COMBINE data are identified only by a subject's COMBINE study identification number and alphanumeric code.
- Under no circumstances should patient identifiers be visible on the MRI media itself or other materials sent to the MRI Core Lab.

6. Data Transfer and Management

a. Clinical Center Workflow

Instructions for Data Transfer are provided to all clinical centers (Appendix vii). Each clinical center will be responsible for recording the recruitment and clinical data it collects. Data entry will be accomplished by filling out the web forms hosted by the DCC's web-based system. The study coordinator is responsible for recruitment of the MRI COMBINE study participant's. Upon recruitment, the study coordinator will fill out sections 1-8 of the 'Cardiac and BOLD Renal MRI Submission Form #291-COMBINE' and at the time of the MRI scan the technologist is responsible for filling out numbers 10-19 of the form. The form is available at

http://qhsapps.ccf.org/ckdp/open_webdocs/Forms/Form291.pdf

Upon completing the MRI scan of a participant, the clinical center MRI technologist will provide the Form 291 to the study coordinator for data entry and send the study to the MRI Core Lab via electronic data transfer.

b. Electronic Data Transfer Instructions

The MRI Core Lab uses Northwestern Memorial Hospital resources for secure data transfer. The software called lifeIMAGE makes it possible to upload and share medical images using a web-based application. The Cardiac MRI Core Lab at Northwestern University (NURAD4D) will receive all images and distribute the renal part to the renal MRI core lab (NorthShore) through lifeIMAGE. Every imaging site will be set up with a username and password to login to lifeIMAGE. In order to be able to do this, every clinical site has to provide a designated person at their institution responsible for the data transfer. Ideally, this should be the MRI technologist performing the scans.

c. Data Transfer via Mail

In case electronic transfer is not an option for a site, please send the anonymized data on a secured CD/DVD via secured mail. In this case please contact the CMRSC for further details.

d. Data report from the DCC

As soon as the study coordinator key enters the Form 291, the DCC will send the MRI core a report including all data collected on the Form 291 plus previously collected data from the database, that is, the data elements listed on the last page of the form.

7. Image Quality Review

Once MRI studies are received at the MRI Core Lab, they will be transferred to our HIPPA compliant archive system and will be checked for image quality. The cardiac images will be validated by NURAD4D and the renal images will be validated by NorthShore. NURAD4D will have to transfer the received renal images to NorthShore via the above mentioned lifeIMAGE. The results of Cardiac Image Quality Assessment will be key entered into form 701 at NURAD4D.

http://qhsapps.ccf.org/ckdp/open_webdocs/Forms/Form701.pdf

Cardiac studies which i) have sufficient resolution for diagnosis, and ii) have little to no artifact, will be considered to be of acceptable image quality and will be analyzed by NURAD4D numbers that will be calculated from the analysis done by NURAD4D will be calculated by the DCC (in indexing by body surface area and EA ratio) for the cardiac images. Also NorthShore will evaluate resolution and artifacts following the same procedure once NURAD4D forwards the renal part of the study.

The results of Renal MRI Image Quality Assessment will be assessed at NorthShore and key entered into Form 702 at NorthShore.

http://qhsapps.ccf.org/ckdp/open_webdocs/Forms/Form702.pdf

The images will also be verified against the respective participant's corresponding information entered into the DCC's online data captured system.

a. Incomplete and Un-interpretable Cardiac Image-sets:

If the image-set is incomplete (e.g. missing images), the MRI Core Lab will tag the study as 'incomplete' in the participant's electronic file in the online database. The MRI Core Lab will also send a notification to the site. The site is expected to respond by re-sending the complete image-set within 72 hours.

If after a response from the MRI Site, the study is still considered un-interpretable due to poor image quality, the MRI Core Lab will tag the study as 'unacceptable' in Form 701 – Core Receipt of Cardiac MRI. The MRI Core Lab(s) will display the reasons why the study (with respect to of the scan) was found to be unacceptable and will include recommendations from MRI Core Lab(s) personnel on how to prevent the problem from occurring again.

If two consecutive MRI studies submitted by a site are found to be of unacceptable quality, the local MRI Site, the Clinical Center Principal Investigator, and the DCC will receive an email notification recommending additional training/assistance for the site.

b. Incomplete and Un-interpretable Renal Image-sets:

If the image-set is incomplete (e.g., missing images), the renal MRI Core Lab will tag the study as 'incomplete' in the participant's electronic file in the online database. The renal MRI Core Lab will also send a notification to the site and the cardiac MRI Core Lab. The site is expected to respond by re-sending the complete image-set within 72 hours.

If after a response from the MRI Site, the study is still considered un-interpretable due to poor image quality, the renal MRI Core Lab will tag the study as 'unacceptable' in Form 702 – Core Receipt of Renal MRI. The MRI Core Lab(s) will display the reasons why the study (with respect to of the scan) was found to be unacceptable and will include recommendations from MRI Core Lab(s) personnel on how to prevent the problem from occurring again.

If two consecutive MRI studies submitted by a site are found to be of unacceptable quality, the local MRI Site, the Clinical Center Principal Investigator, and the DCC will receive an email notification recommending additional training/assistance for the site.

8. Image Analysis

Reading and analysis of MRI datasets from all participants will be performed at Northwestern and NorthShore MRI Core Labs. The analyses will be carried out by specially trained personnel. The MRI Core Lab Directors and Radiologists will be responsible for supervising image analysis personnel to verify compliance with the Image Analysis Protocol. The turn-around time from receipt of the entire data-set (images, associated text information, participant data required for image analysis, and confirmation of informed consent.) from a clinical center, to data entry of results in the study database at the DCC is estimated at 10 business days. Cardiac MRI results will be key-entered into Form 721:

http://qhsapps.ccf.org/ckdp/open_webdocs/Forms/Form721.pdf

Renal MRI results will be entered into Form 722:

http://qhsapps.ccf.org/ckdp/open_webdocs/Forms/Form722.pdf

a. Methods

Left ventricular (LV) mass, end-diastolic volume, end-systolic volume and ejection fraction will be measured on short-axis cine image series. The epicardial and endocardial borders of the LV will be automatically generated by the software and manually adjusted by the user on each short-axis slice at end-diastole and at end-systole, and values for the above parameters (absolute value as well as normalized to body surface area) will then be automatically generated by the software. Left atrial (LA) volume and output will be determined using similar methods. Calculation of flow and velocity parameters (e.g. mean, and max velocity, mean, cumulative, prograde, retrograde flow) for the mitral valve will also be performed.

For renal BOLD and Diffusion MRI analysis, standard regions of interest (ROI) analysis will be performed on R2* and ADC maps. While we anticipate most sites will have the capability for inline mapping, we will use offline mapping using Matlab where needed. The ROI analysis will be carried out on the Siemens workstation. The ROIs in the cortex and medulla for BOLD MRI will be defined using the first image of the 8 echoes and then copied to the R2* map. Typically the ROIs will contain at least 20 pixels. Based on our experience to-date, there is not adequate contrast between cortex and medulla on the ADC maps and so only value will be reported.

Once the analysis has been completed, the results will be reviewed by a specialized imaging physician and/or trained imaging fellow at the MRI Core Lab for accuracy of contours. Personnel responsible for generating contours (Analyzers) and approving contours (Physician Over-readers) have sufficient training to ensure proficiency in performing image analysis in an accurate and reproducible manner. Trial specific measurements of inter-observer and intra-observer reproducibility procedures have been established at Northwestern University and NorthShore to ensure efficiency, reproducibility and expertise for our personnel. Staff training occurs at the beginning of employment and annually thereafter.

As the COMBINE study evolves, it is expected that newer software packages may become available for the semi-automated analysis of the image sets for measurement of left atrial volume as well as LV function. When these become available, analyses using these new software packages will be compared with the contouring method described above. If the new

method offers advantages such as increased throughput and good statistical agreement for quantitative results by the new method and the established method can be demonstrated, the new analysis software will be used to analyze the image sets during the remainder of the study.

9. Reporting of Image Analysis Results

As noted, Cardiac MRI results will be key entered into Form 721.

http://qhsapps.ccf.org/ckdp/open_webdocs/Forms/Form721.pdf

The following is a list of parameters which will be reported for each **cardiac** participant.

- LV ejection fraction (%)
- LV end-diastolic (ED) volume, and end-systolic (ES) volume (ml)
- LV ED and ES volumes indexed to BSA (ml/m^2) (to be calculated by the DCC)
- LV stroke volume (ml)
- stroke volume indexed to BSA (ml/m^2) (to be calculated by the DCC)
- Cardiac Output (l/min)
- Cardiac Index ($\text{l}/\text{min}/\text{m}^2$) (to be calculated by the DCC)
- LV mass at ED (g)
- LV mass at ED indexed to BSA (g/m^2) (to be calculated by the DCC)
- Anterior, septal and posterior LV wall thickness at base/mid/apex (mm)
- Flow assessment at Mitral Valve:
 - E and A velocity (cm/sec)
 - E/A ratio
 - forward/reverse flow
 - net flow (ml/cycle)
 - net flow indexed to BSA ($\text{ml}/\text{cycle}/\text{m}^2$) (to be calculated by the DCC)

As noted, Renal MRI results will be entered into Form 722.

http://qhsapps.ccf.org/ckdp/open_webdocs/Forms/Form722.pdf

The following is a list of parameters which will be reported for each **renal** patient (averaged over all slices and Right and Left kidneys).

- ADC ($10^{-3} \text{ mm}^2/\text{s}$)
- R2* cortex (s^{-1})
- R2* medulla (s^{-1})
- R2* cortex _post furosemide (s^{-1})
- R2* medulla post furosemide (s^{-1})

The form notes whether the results come from the right kidney, the left kidney, or both.

10. Quality Assurance and Quality Control of Image Acquisition

Quality assurance refers to the steps taken prior to data acquisition to assure accuracy and to minimize errors. Quality control refers to the steps taken after data are collected to examine quality, particularly to measure reproducibility, and to identify and address errors.

For the COMBINE study, Quality Assurance measures performed by the MRI Core Lab(s) include support of MR technologists for the image acquisition protocol, MRI technologist certification, MRI Qualification of the sites, and ongoing monitoring of performance of each Field Center. Quality Control measures include identification and resolution of problems that arise with respect to MR data-set acquisition, transfer, image quality, and data management.

a. MRI Qualification of sites and Quality Assurance for Image Acquisition

In order to document minimum competency, each site will be requested to submit two studies for evaluation by the MRI Core Lab(s), which will be deemed 'acceptable' or 'unacceptable' based on specific criteria for image quality (as described in Section 4). When studies are found to be acceptable the site is validated for performing MRI exams for COMBINE. When one or both studies are found to be unacceptable, the site is requested to submit an additional study after modifying their image acquisition method as recommended. If this additional study is also found to be unacceptable, the site will receive a recommendation to undergo training before they can start enrolling study participants.

b. MRI Core Lab Review of Images

Once uploaded to the MRI Core Lab(s) archive, each image-set will be reviewed by a specialized imaging physician or trained fellow or research associates. Image-sets will be checked for completeness, then contoured and processed by trained research associates. The original and the contoured images will be assessed by a trained physician and scored with respect to overall diagnostic acceptability and will be tagged as 'acceptable' or 'unacceptable' for COMBINE Study analysis. The physician will also be responsible to report incidental findings to the DCC using form 711 and 712. The acceptance of image sets will be communicated to the COMBINE Study DCC.

11. Cardiac & Renal MRI Training and Additional Site Support

If sites require additional support for acquiring MRI data, the MRI Core Lab(s) will recommend and coordinate the provision of training to these sites.

Training and support will be requested by the respective MRI Core Lab(s) (contingent on cardiac and/or renal imaging assistance) for sites, which did not qualify initially; i.e. one or both validation studies were unacceptable and even recommendations for modifying their image acquisition method did not produce an acceptable image-set. A site which initially qualified, but later appears to be having difficulty with image acquisition (i.e. two consecutive image-sets sent by the site are found to be unacceptable) will also receive a recommendation for training.

In case the site has a change in one or both of the two certified trained personnel, the site has to report this change to the MRI Core Labs. In addition, the site has to identify a new MRI technologist for the study. The new MRI technologist will then need to get certified following the

steps outlined in chapter 4a and providing a test case using the MRI submission form 291.

Training can be supplemented via screen sharing detailing the steps for image acquisition. Screen sharing will be employed in order to troubleshoot common or recurring questions or problems that become manifest during the trial.

Should additional training initiatives prove necessary in the case of certain sites, two approaches may be mediated by the MRI Core Lab contingent upon access capability from the site to use the Siemens remote login software Expert-I. Technologists may undergo training at the designated center (e.g., Northwestern) or software tools may be implemented for 'remote assistance' over the internet.

Remote Assistance is a desirable feature for online, interactive, internet-mediated support of the MRI technologists from the core lab or designated training site. The goal is to offer real-time technical expertise to sites requesting or requiring additional support or training. It is expected that this 'hands-on' approach would be very efficient for training technologists and providing interactive guidance until they are fully independent. Remote assistance may not be available at the start of the trial, but should become available during the course of the trial.

Please note: For cardiac related questions regarding data acquisition and analysis please contact NURAD4D. In addition, for renal related questions regarding data acquisition and analysis please contact NorthShore. The contact information can be found here:

http://ghsapps.ccf.org/ckdp/open_webdocs/AddressDirectory/CKDAddressDirectory.pdf

11. Appendices

- i. Image Acquisition Protocol
- ii. Instructions for COMBINE Study Cardiac Imaging (Cine series)
- iii. Instructions for Combine Study Cardiac Flow Imaging (Phase Contrast)
- iv. Instructions for COMBINE Study Renal Imaging
- v. COMBINE Study Cardiac Sequence Parameters
- vi. COMBINE Study Renal Sequence Parameters
- vii. Data Transfer Instructions

i. Image Acquisition Protocol

Recommended steps for Image Acquisition and the MR sequence parameters for the protocol are given below.

a. Cardiac Participant Preparation

1. Complete Participant MRI Safety and Study Participation Consent Documentation
2. Inform the participant about the breath-holding steps and have them practice.
3. Breath-holding instructions: "Breath in ... breathe out ... breathe in and hold your breath".
4. **Request them to use the rest room before the study.**
5. Prepare the table with Cardiac & Abdominal Coil. However, if only one coil is available reposition for renal.
6. Use ECG Instructions to hook up the electrodes (use VCG, as available).

b. Renal Participant Preparation

7. The research study coordinator should contact the participant two days prior to the scan to remind the participants the following instructions:
 - Participants should fast for 4-6 hours prior to exam
 - Participants should be instructed to bring a snack to have following the scan
 - The following medications adjustments will be needed for certain participants:
 - NSAIDs should not be taken for three days prior to the renal MRI scan. If necessary, aspirin could be used.
 - Doses of insulin should be halved on the day of the renal MRI scan due to fasting.
 - ACEi/ARBs should be taken after the renal MRI scan.
 - Furosemide should be held the day of the MRI scan.
8. A nurse or physician will need to be available for the Furosemide injection.
9. Place a 22 ga. cannula in an ante-cubital vein.
10. Inform the participant about the breath-holding steps and have them practice
11. Breath-holding instructions: "Breath in ... breathe out ... breathe in and hold your breath".
12. Have nurse or physician prepare a dose for IV administration of 20mg of Furosemide. Remind the subject regarding the diuresis for few hours following administration and instruct to intake fluids.

c. Image Acquisition

13. Enter data required in **MRI Submission Form**
14. Perform **multi-planar Scouts/Localizers** for chest: Position ISOCENTER at Heart
Cine-images:
 - Steady state free precession (SSFP) sequence
 - parallel imaging (GRAPPA) with an acceleration factor of 2 to reduce acquisition time (optional)
 - Slice thickness for atria: 5 mm; with 0 Gap for short-axis slices
 - Slice thickness for ventricle: 8 mm; with 0 Gap for short-axis slices
 - 2 overlapping stacks of short axis slices through left atrium and left ventricle
 - For left atrium make sure to cover beyond the tip of the leaflets of mitral valve in diastole

- For left ventricle cover from base to apex
- Acquire 2 slices per breath-hold, as tolerated.
- 2-chamber Vertical long axis view
- 4-chamber Horizontal long axis view (multi-slice through entire heart)
- 3-chamber Left-ventricular outflow tract
- 4-chamber 2D Flow PC-MRI (in plane for visualization of mitral valve) with recommended 80ms VENC.
- 2D Flow PC-MRI at mitral valve (Through-plane at mitral valve) with recommended 80ms VENC.

Renal-images:

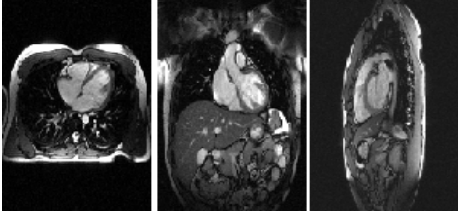
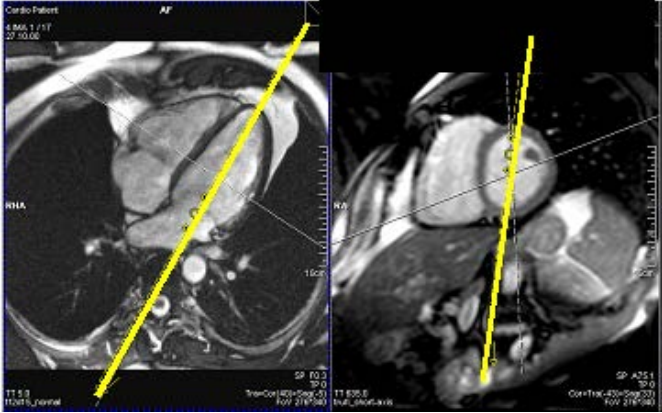

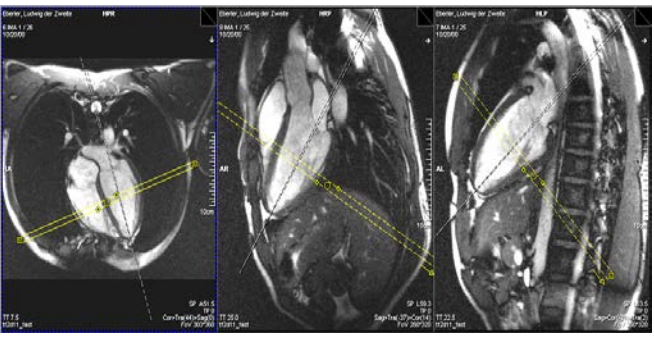
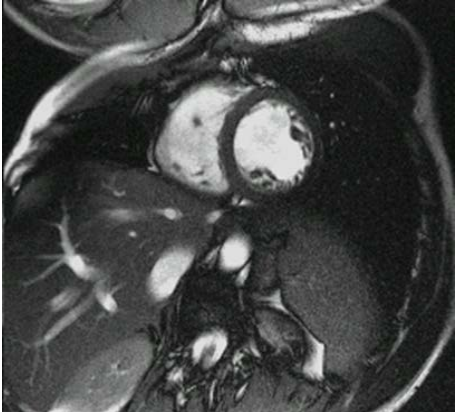
- Reposition at ISOCENTER for Renal
- Perform **multi-planar Scouts/Localizers** for renal imaging.
- Diffusion Coronal non-breath-hold MRI:
 - shallow breathing consistently throughout scan
 - 5 b values 200 – 1000 s/mm² with diffusion gradients along each principle direction to allow calculation of Trace and ADC
- BOLD Coronal Breath-hold MRI: Multiple GRE sequence with 8 echoes to allow for R2* mapping
 - Instruct subject importance of consistency of breath-hold
- Inject Furosemide 20 mg / 2 ml
- Repeat-BOLD Coronal Breath-hold MRI:
 - Multiple GRE sequence with 8 echoes
 - Instruct subject importance of consistency of breath-hold
 - **maximum 15 minutes post furosemide or until subject needs to void**

17. **Submit image-set to MRI Core Lab** as per Data Transfer Instructions.

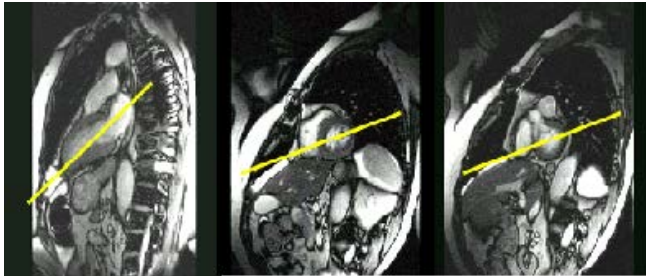
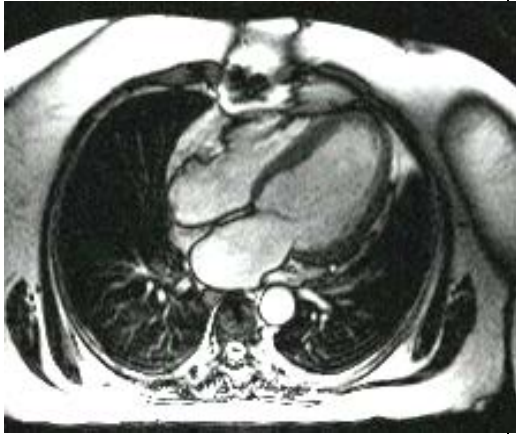
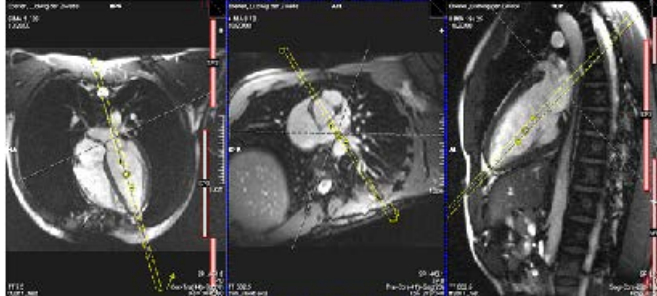
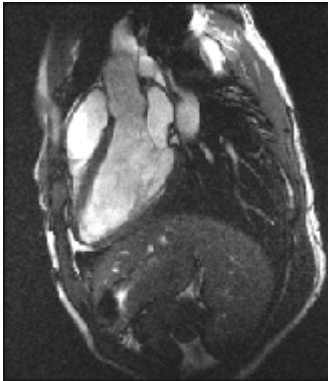
18. **Enter data** recorded on the hard-copy Cardiac and BOLD Renal MRI Submission form into the '**Cardiac and BOLD Renal MRI Submission Form #291**'

http://ghsapps.ccf.org/ckdp/open_webdocs/Forms/Form291.pdf


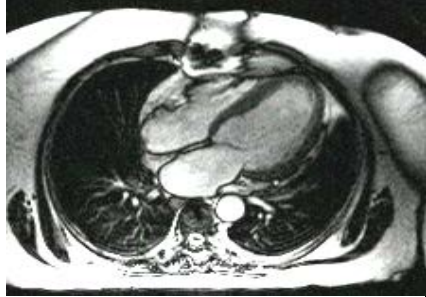
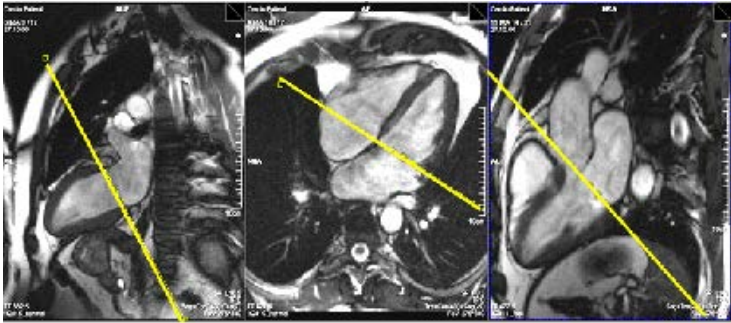
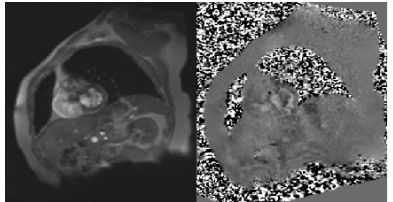
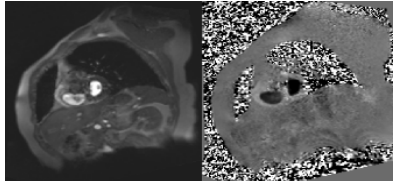
ii. Instructions for COMBINE Study Cardiac Imaging (Cine series)

Series	Prescription	Image example
<p>Three plane localizer</p>	<p>Key to make sure that the coil coverage is optimal and the Heart is approximately in the center of the coverage.</p>	 <p>Axial Coronal Sagittal</p>
<p>2-Chamber Vertical Long Axis Breathhold</p>	<p>LV apex in 4-chamber view, Mid-mitral valve in 4-chamber view, Mid-LV chamber in short axis view Parallel to ventricular septum</p>  <p>Use large enough FOV to avoid wrap in phase direction</p>	 <p>2-Chamber View</p>
<p>Short Axis Breathhold</p>	<p>Optimal localization perpendicular to all 3 long axis views. 2 overlapping stacks to cover atria & ventricle</p>  <p>Use large enough FOV to avoid wrap in phase direction, acquire 2 stack short axis image stacks covering the entire left ventricle AND left atrium</p>	 <p>Short Axis View</p>

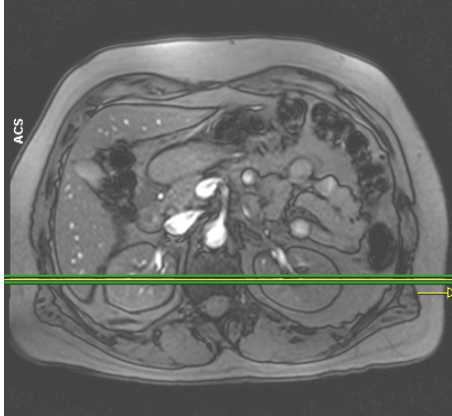
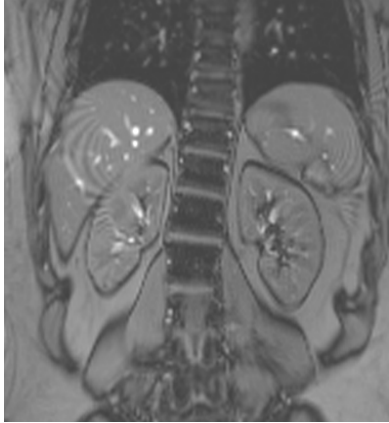
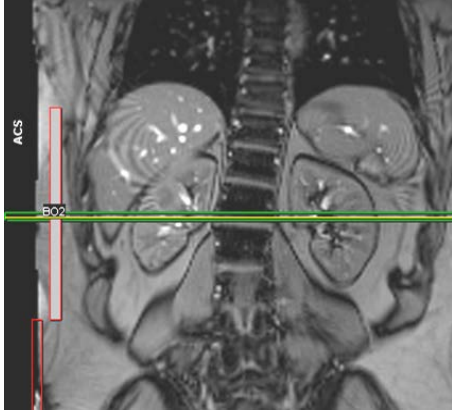

continued: Instructions for COMBINE Study Cardiac Imaging (Cine series)

Series	Prescription	Image example
<p>4-Chamber Horizontal Long Breathhold</p>	<p>Parallel to long axis in 2-chamber view, through RV apex and mid-LV chamber in short axis view (yellow arrow), Avoid LV outflow tract in short axis view</p>  <p>Use large enough FOV to avoid wrap in phase direction (multi-slice covering entire heart)</p>	 <p>4-Chamber View</p>
<p>3-Chamber Left Ventricular Outflow Breathhold</p>	<p>Parallel to long axis and through LV apex in two views Bisect LV outflow tract in short axis view</p>  <p>Use large enough FOV to avoid wrap in phase direction</p>	 <p>3-Chamber View</p>

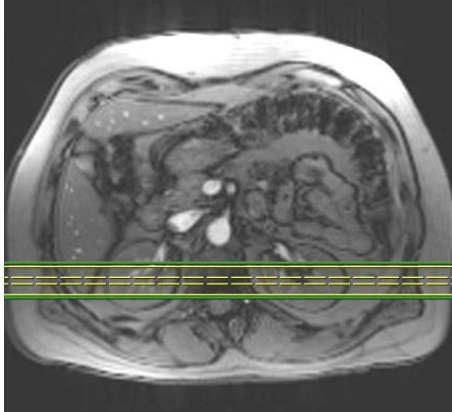
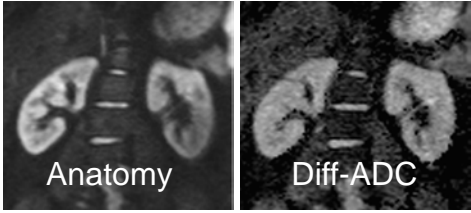
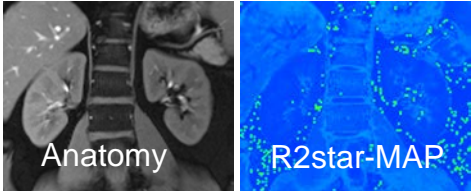
iii. Instructions for COMBINE Study Cardiac Flow Imaging (Phase Contrast)

Series	Prescription	Image example
<p>4-Chamber Horizontal Long Breathhold</p>	<p>Position across mitral valve in 2-chamber, 3-chamber, & 4-chamber orthogonal views</p>  <p>Use large enough FOV to avoid wrap in phase direction</p>	 <p>4-Chamber flow quantification</p>
<p>Mitral Valve Breathhold</p>	<p>Position across mitral valve in 2-chamber, 3-chamber, & 4-chamber orthogonal views</p>  <p>Use large enough FOV to avoid wrap in phase direction</p>	 <p>Closed Mitral Valve</p>  <p>Open Mitral Valve</p>

iv. Instructions for COMBINE Study Renal Imaging

Series	Prescription	Image example
Two plane localizer	<p>Protocol includes one, but the site is free to choose others.</p> <p>Key to make sure that the coil coverage is optimal and the kidneys are approximately in the center of the coverage.</p>	
Coronal localizer_breathhold	<p>Protocol includes one, but the site is free to choose others.</p> <p>To obtain optimal coronal slice</p> 	
Axial localizer_breathhold	<p>Protocol includes one, but the site is free to choose others.</p> <p>To use for prescribing BOLD and DWI scans</p> 	

Continued: Instructions for COMBINE Study Renal Imaging

<p>Coronal_DWI</p>		 <p>Anatomy Diff-ADC</p> <p>Note cropped to fit</p>
<p>Coronal_BOLD_BH</p>	<p>Same as above. Copy slice positions.</p> <p>Due to the dependence of $R2^*$ values on the voxel size, it is preferred to NOT change the FOV and matrix size between subjects. So we have chosen a sufficiently large FOV to fit most participants. The key is to remember not to make it smaller to fit smaller subjects. The matrix size was chosen to make the breath hold interval ~12s which is reasonable for most subjects. We do not use parallel imaging because it increases the acquired voxel size.</p> <p>If for any reason, a different setting is used, then make sure to use the same for the 12 month scan.</p>	 <p>Anatomy R2star-MAP</p> <p>Note cropped to fit</p>

v. COMBINE Study Cardiac Sequence Parameters

COMBINE_cardiac MRI protocol_3T Skyra					
Cine Series	Perform multi-planar scout/localizer scans				
Plane	2 Plane	Short Axis LA	Short Axis LV	4-Chamber	3-Chamber
Pulse sequence	True FISP	True FISP	True FISP	True FISP	True FISP
Repetition Time (TR/ms)	28.80	28.80	28.80	28.80	28.80
Echo Time (TE/ms)	minimized	minimized	minimized	minimized	minimized
Flip Angle (FA/°) (Maximize)	≥ 90°	≥ 90°	≥ 90°	≥ 90°	≥ 90°
Field of View (FOV/mm) (depending on subject size)	read 400 mm * 100% phase	read 400 mm * 100% phase	read 400 mm * 100% phase	read 400 mm * 100% phase	read 400 mm * 100% phase
Spatial Resolution (mm)	1.3x1.3x10.0	1.3x1.3x10.0	1.3x1.3x10.0 mm	1.3x1.3x10.0 mm	1.3 x 1.3 x 10.0
Image Matrix (pixel)	> 128 x 256	> 128 x 256	> 128 x 256	> 128 x 256	> 128 x 256
Slice Thickness (mm)	8	5	8	8	8
Slice Gap (% mm)	0	0	0	0	0
Number of Slices	1	~6	~10	~6	1
Bandwidth (Hz/pixel)	1488	1488	1488	1488	1488
Parallel Imaging acceleration factor	GRAPPA: 2	GRAPPA: 2	GRAPPA: 2	GRAPPA: 2	GRAPPA: 2
Partial Fourier (if any)	off	off	off	off	off
Gating	ECG/Retro	ECG/Retro	ECG/Retro	ECG/Retro	ECG/Retro
Number of Segments	~25	~25	~25	~25	~25
Breathhold (s)	≤ 15	≤ 15	≤ 15	≤ 15	≤ 15
Flow Quantification					
Flow Series	Perform multi-planar scout/localizer scans				
Plane	4-Chamber In-plane		Mitral Valve Through-Plane		
Pulse sequence	Flash		Flash		
Repetition Time (TR/ms)	36.80		36.80		
Echo Time (TE/ms)	4.6		4.6		
Flip Angle (FA/°) (Maximize)	≥ 30°		≥ 30°		
Field of View (FOV/mm) (depending on subject size)	read 450 mm * 75 % phase		read 450 mm * 75 % phase		
Spatial Resolution (mm)	2.0 x 2.0 x 7.0		2.0 x 2.0 x 7.0		
Image Matrix (pixel)	192 x 192		192 x 192		
Slice Thickness (mm)	7		7		
Slice Gap (% mm)	20%		20%		
Number of Slices	1		1		
Bandwidth (Hz/pixel)	496		496		
Parallel Imaging acceleration factor	GRAPPA: 2		GRAPPA: 2		
Gating	ECG/Retro		ECG/Retro		
Number of Segments	4		4		
Breathhold (s)	≤ 18		≤ 18		
venc	~80ms		~80 ms		

continued: COMBINE Study Cardiac Sequence Parameters

COMBINE_cardiac MRI protocol_3T Verio					
Cine Series	Perform multi-planar scout/localizer scans				
Plane	2 Plane	Short Axis LA	Short Axis LV	4-Chamber	3-Chamber
Pulse sequence	True FISP	True FISP	True FISP	True FISP	True FISP
Repetition Time (TR/ms)	445.40	445.40	445.40	445.40	445.40
Echo Time (TE/ms)	minimized	minimized	minimized	minimized	minimized
Flip Angle (FA/°) (Maximize)	≥ 65°	≥ 65°	≥ 65°	≥ 65°	≥ 65°
Field of View (depending on subject size)	read 400 mm * 100% phase	read 400 mm * 100% phase	read 400 mm * 100% phase	read 400 mm * 100% phase	read 400 mm * 100% phase
Spatial Resolution (mm)	3.0 × 2.1×8.0	3.0 × 2.1 × 8.0	3.0 × 2.1× 8.0	3.0× 2.1 × 8.0	3.0 × 2.1 × 8.0
Image Matrix (pixel)	> 128 × 256	> 128 × 256	> 128 × 256	> 128 × 256	> 128 × 256
Slice Thickness (mm)	8	5	8	8	8
Slice Gap (% mm)	0	0	0	0	0
Number of Slices	1	~6	~10	~6	1
Bandwidth (Hz/pixel)	1488	1488	1488	1488	1488
Parallel Imaging acceleration factor	GRAPPA: 2	GRAPPA: 2	GRAPPA: 2	GRAPPA: 2	GRAPPA: 2
Partial Fourier (if any)	off	off	off	off	off
Gating	ECG/Retro	ECG/Retro	ECG/Retro	ECG/Retro	ECG/Retro
Number of Segments	~25	~25	~25	~25	~25
Breathhold (s)	≤ 15	≤ 15	≤ 15	≤ 15	≤ 15
Flow Quantification					
Flow Series	Perform multi-planar scout/localizer scans				
Plane	4-Chamber In-plane			Mitral Valve Through-Plane	
Pulse sequence	Flash			Flash	
Repetition Time (TR/ms)	54.80			54.80	
Echo Time (TE/ms)	3.74			3.74	
Flip Angle (FA/°) (Maximize)	≥ 25°			≥ 25°	
Field of View (FOV/mm) (depending on subject size)	read 450 mm * 75 % phase			read 450 mm * 75 % phase	
Spatial Resolution (mm)	2.4 x 1.8 x 6.0			2.4 x 1.8 x 6.0	
Image Matrix (pixels)	192 × 192			192 × 192	
Slice Thickness (mm)	6			6	
Slice Gap (% mm)	20%			20%	
Number of Slices	1			1	
Bandwidth (Hz/pixel)	496			496	
Parallel Imaging acceleration factor	GRAPPA: 2			GRAPPA: 2	
Gating	ECG/Retro			ECG/Retro	
Number of Segments	4			4	
Breathhold (s)	≤ 18			≤ 18	
venc	80ms			80ms	

continued: COMBINE Study Cardiac Sequence Parameters

COMBINE_cardiac MRI protocol_1.5 Avanto					
Cine Series	Perform multi-planar scout/localizer scans				
Plane	2 Plane	Short Axis LA	Short Axis LV	4-Chamber	3-Chamber
Pulse sequence	True FISP	True FISP	True FISP	True FISP	True FISP
Repetition Time (TR/ms)	445.40	445.40	445.40	445.40	445.40
Echo Time (TE/ms)	minimized	minimized	minimized	minimized	minimized
Flip Angle (FA/°) (Maximize)	≥ 65°	≥ 65°	≥ 65°	≥ 65°	≥ 65°
Field of View (FOV/mm) (depending on subject size)	read 400 mm * 100% phase	read 400 mm * 100% phase	read 400 mm * 100% phase	read 400 mm * 100% phase	read 400 mm * 100% phase
Spatial Resolution (mm)	3.0 x 2.1 x 8.0	3.0 x 2.1 x 8.0	3.0 x 2.1 x 8.0	3.0 x 2.1 x 8.0	3.0 x 2.1 x 8.0
Image Matrix	> 128 * 256	> 128 * 256	> 128 * 256	> 128 * 256	> 128 * 256
Slice Thickness (mm)	8	5	8	8	8
Slice Gap (mm)	0	0	0	0	0
Number of Slices	1	~6	~10	~6	1
Bandwidth (Hz/pixel)	1488	1488	1488	1488	1488
Parallel Imaging acceleration factor	GRAPPA: 2	GRAPPA: 2	GRAPPA: 2	GRAPPA: 2	GRAPPA: 2
Partial Fourier (if any)	off	off	off	off	off
Gating	ECG/Retro	ECG/Retro	ECG/Retro	ECG/Retro	ECG/Retro
Number of Segments	~25	~25	~25	~25	~25
Breathhold (s)	≤ 15	≤ 15	≤ 15	≤ 15	≤ 15
Flow Quantification					
Flow Series	Perform multi-planar scout/localizer scans				
Plane	4 Chamber-Inplane		Mitral Valve Through-Plane		
Pulse sequence	Flash		Flash		
Repetition Time (TR/ms)	54.80		54.80		
Echo Time (TE/ms)	3.74		3.74		
Flip Angle (FA/°) (Maximize)	≥ 25°		≥ 25°		
Field of View (FOV/mm) (depending on subject size)	read 450 mm * 75 % phase		read 450 mm * 75 % phase		
Spatial Resolution (mm)	2.4x1.8x6.0		2.4x1.8x6.0		
Image Matrix	192*192		192*192		
Slice Thickness (mm)	6 mm		6 mm		
Slice Gap (% mm)	20%		20%		
Number of Slices	1		1		
Bandwidth (Hz/pixel)	496		496		
Parallel Imaging acceleration factor	GRAPPA: 2		GRAPPA: 2		
Gating	ECG/Retro		ECG/Retro		
Number of Segments	4		4		
Breathhold (s)	≤ 18		≤ 18		
venc	80ms		80ms		

vi. COMBINE Study Renal Sequence Parameters

COMBINE_renal MRI protocol_3T Skyra					
Series	Localizer			DWI	BOLD
Plane	2 Plane	Coronal	Axial	Coronal	Coronal
Pulse sequence	gre	gre	gre	ep2d_diff	gre
TR/ms	7	7	7	3000	61
TE/ms	2.66	2.66	2.66	78	4.92, 9.84, 14.76, 19.68, 24.6, 29.52, 34.44, 39.36
Read out mode	n/a	n/a	n/a	n/a	Bipolar
In line mapping	n/a	n/a	n/a	Trace wtd. Images; ADC Maps	T2* (VB 17)/R2* (VD 13) Map
BW Hz/pixel	290	290	290	1532	260
FOV mm	400	400	400	400	400
Slices	3 ax, 3 cor	5	5	5	5
Concatenation	6	5	5	1	5
Slice Thickness / mm	8	8	8	5	5
Skip	50%	50%	50%	0	0
Fat suppressed	No	No	No	Fat Sat	Fat Sat
Parallel Imaging acceleration factor	None	None	None	2	None
Diffusion mode	n/a	n/a	n/a	3-Scan Trace	n/a
B value s/mm ²	n/a	n/a	n/a	200, 300, 500, 700, 1000	n/a
Diff. gradients	n/a	n/a	n/a	Bipolar	n/a
NEX	2	2	2	5	1
Acq-matrix	154x256	154x256	154x256	192x192	
Flip angle/degrees	20	20	20	90	30
Typ. Scan time m:s	0:14	0:07	0:07	3:54	1:00 (5 slices)
Options/comments	Site preference			Instruct subjects to not to take deep breaths.	Changing FOV and/or matrix size not preferred

Abbreviations: SSFP: steady state free precession, VLA: vertical long axis view, LVOT: left-ventricular outflow tract view, GRE: gradient recalled echo.

continued: COMBINE Study Renal Sequence Parameters

COMBINE_renal MRI protocol_3T Verio					
Series	Localizer			DWI	BOLD
Plane	2 Plane	Coronal	Axial	Coronal	Coronal
Pulse sequence	gre	gre	gre	ep2d_diff	gre
TR/ms	7	7	7	3000	61
TE/ms	2.66	2.66	2.66	78	4.92, 9.84, 14.76, 19.68, 24.6, 29.52, 34.44, 39.36
Read out mode	n/a	n/a	n/a	n/a	Bipolar
In line mapping	n/a	n/a	n/a	Trace wtd. Images; ADC Maps	T2* (VB 17)/R2* (VD 13) Map
BW Hz/pixel	290	290	290	1532	260
FOV mm	400	400	400	400	400
Slices	3 ax, 3 cor	5	5	5	5
Concatenation	6	5	5	1	5
Slice Thickness / mm	8	8	8	5	5
Skip	50%	50%	50%	0	0
Fat suppressed	No	No	No	Fat Sat	Fat Sat
Parallel Imaging acceleration factor	None	None	None	2	None
Diffusion mode	n/a	n/a	n/a	3-Scan Trace	n/a
B value s/mm ²	n/a	n/a	n/a	200, 300, 500, 700, 1000	n/a
Diff. gradients	n/a	n/a	n/a	Bipolar	n/a
NEX	2	2	2	5	1
Acq-matrix	154x256	154x256	154x256	192x192	
Flip angle/degrees	20	20	20	90	30
Typ. Scan time m:s	0:14	0:07	0:07	3:54	1:00 (5 slices)
Options/comments	Site preference			Instruct subjects to not to take deep breaths.	Changing FOV and/or matrix size not preferred

continued: COMBINE Study Renal Sequence Parameters

COMBINE_renal MRI protocol_1.5T Avanto					
Series	Localizer			DWI	BOLD
Plane	2 Plane	Coronal	Axial	Coronal	Coronal
Pulse sequence	gre	gre	gre	ep2d_diff	gre
TR/ms	7	7	7	3000	61
TE/ms	2.66	2.66	2.66	78	4.92, 9.84, 14.76, 19.68, 24.6, 29.52, 34.44, 39.36
Read out mode	n/a	n/a	n/a	n/a	Bipolar
In line mapping	n/a	n/a	n/a	Trace wtd. Images; ADC Maps	T2* (VB 17)/R2* (VD 13) Map
BW Hz/pixel	290	290	290	1532	260
FOV mm	400	400	400	400	400
Slices	3 ax, 3 cor	5	5	5	5
Concatenation	6	5	5	1	5
Slice Thickness / mm	8	8	8	5	5
Skip	50%	50%	50%	0	0
Fat suppressed	No	No	No	Fat Sat	Fat Sat
Parallel Imaging acceleration factor	None	None	None	2	None
Diffusion mode	n/a	n/a	n/a	3-Scan Trace	n/a
B value s/mm ²	n/a	n/a	n/a	200, 300, 500, 700, 1000	n/a
Diff. gradients	n/a	n/a	n/a	Bipolar	n/a
NEX	2	2	2	5	1
Acq-matrix	154x256	154x256	154x256	192x192	
Flip angle/degrees	20	20	20	90	30
Typ. Scan time m:s	0:14	0:07	0:07	3:54	1:00 (5 slices)
Options/comments	Site preference			Instruct subjects to not to take deep breaths.	Changing FOV and/or matrix size not preferred

vii. Data Transfer Instructions

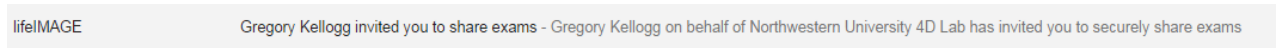
The MRI Core Lab uses Northwestern Memorial Hospital resources for secure and HIPPA compliant data transfer. The software called lifelIMAGE makes it possible to upload and share medical images using a web-based application. The Cardiac MRI Core at Northwestern University (4D Lab) will receive all images and distribute the renal part to the renal MRI core lab (Northshore) through lifelIMAGE. Every imaging site will be set-up with a username and password to login to the lifelIMAGE ReferralBox. In order to be able to do this, every site has to provide a designated person at their institution responsible for the data transfer. Ideally this would be the MRI technologist performing the scans.

In case the site temporarily lacks web access or for any other reason cannot temporarily transfer the measured MRI data electronically, we recommend waiting until the problems are resolved.

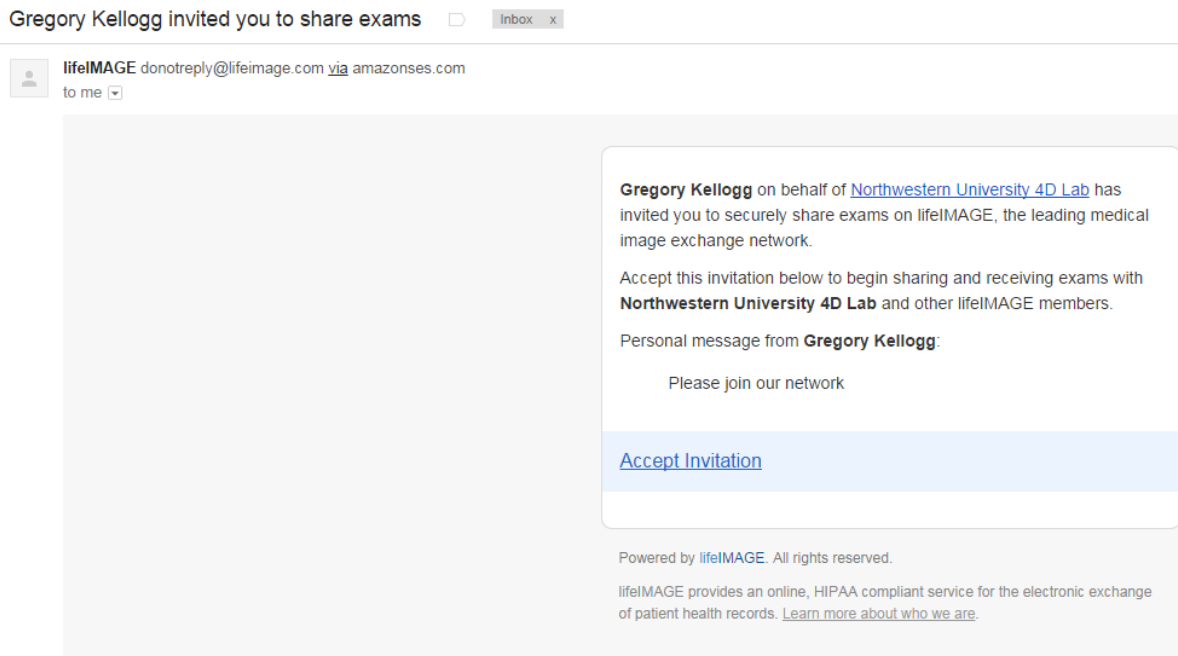
How To Transfer:

Here are the step by step instructions for setting up the account and transferring a study to the MRI Core Labs.

1. You will receive an email from Gregory Kellogg (Northwestern University) inviting you to share exams using lifelIMAGE:



Open email and click on accept invitation:



2. After first time login you (user) must fill out your profile and choose a password.

Welcome to lifeIMAGE

[Gregory Kellogg](#) has invited you to **join the lifeIMAGE Network** and start securely sharing exams today.

lifeIMAGE is a secure, HIPAA-compliant service for electronically exchanging medical images and information.

When you join the network, you will be able to instantly connect with a specialist or department at another facility to send or receive your patient's exams, without them relying on your patient to carry a CD. This will improve care coordination by simplifying information exchange during referral requests and transfers.



Fill out your profile

Step 1 of 2
* = Required field

Let's start with your personal info

* First name:

* Last name:

Set your account's display name

* Display name:

This display name will be used as your network identity.

For example, if you plan to use this account as an individual you can enter your first and last name, or if this account will be used by a group, you can use an institution or group name.

Now, let's set your login credentials

* Email:

This is the email your account will be registered to, if you wish to change it, update the email in the box above.

* Password:

Password must be at least 8 characters long and contain at least one letter and one number.

* Confirm password:

Re-enter the password entered above.

[Next Step](#)

3. A first time user must also choose security questions and answers, so you can reset your password if ever forgotten.
4. At that point you are successfully logged in to lifeIMAGE. First you will see a screen with terms, you need to accept:

lifeIMAGE™

Agree to the terms

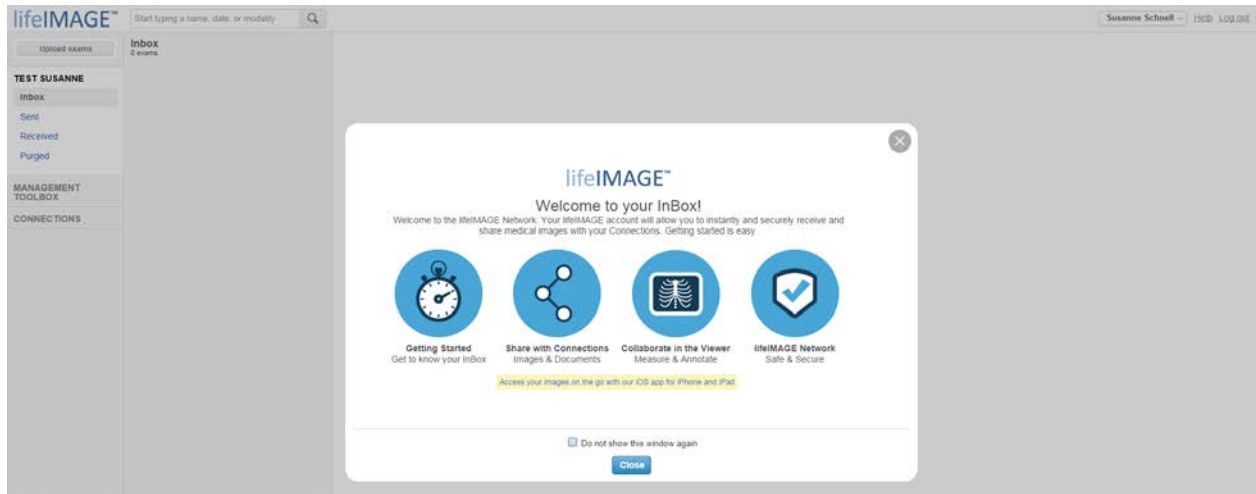
You are about to log in to, or share an exam with, a secure, cloud-based lifeIMAGE account for the continuing care and treatment of one or more patients. The imaging examination and associated patient information that you will send or receive will be transferred and stored in accordance with HIPAA standards on a secure server.

By clicking the accept button, you acknowledge and agree to the following:

- You have the authority and the right, on behalf of your institution, to share the imaging examination and protected health information (PHI) of the associated patients.
- You have obtained any required consents, authorizations, or other permissions necessary to share the image and associated patient information and have otherwise taken steps to ensure that the transmission complies with applicable law.
- You are adhering to all international, national and/or state laws/regulations that govern the imaging exam and associated PHI.
- Sharing imaging examination and associated PHI is for purposes of continuity of care and not for any illegal or malicious purpose.
- lifeIMAGE is not the intended recipient of any imaging examination, rather, lifeIMAGE provides a conduit for the transfer of imaging examinations from one health care provider to another.
- lifeIMAGE is not a healthcare provider and is not responsible for the medical care or treatment of any patient.
- You agree to hold lifeIMAGE harmless from any costs or damages arising from your use, misuse or reliance on this system, except to the extent that such costs or damages are caused by lifeIMAGE's negligence or intentional misconduct.

[Accept](#)

5. Welcome to your InBox:

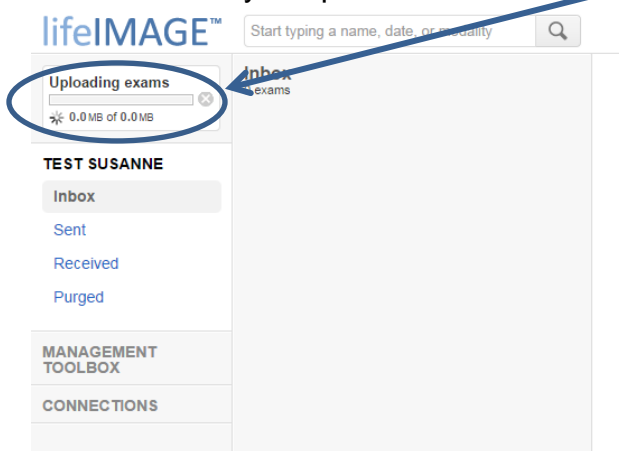


6. Once this is done you will receive another email in your mailbox to welcome you to lifeIMAGE. This email will also provide a link to the login page. It would make sense if you bookmarked this login page in your browser.
7. Now you can log in to upload dicom exams to lifeIMAGE from CD. For this click **Upload Exams** in the top left corner to begin the upload process.

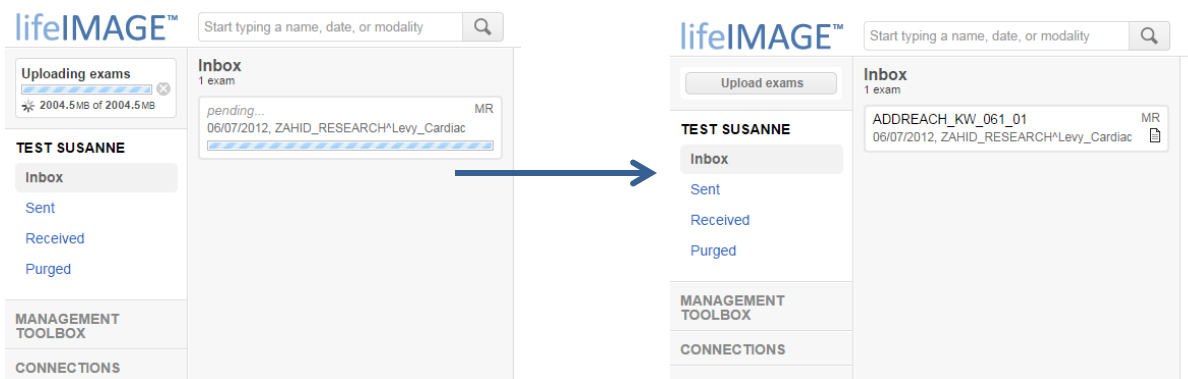
Step 1. Insert your CD or DVD and then click **Find exams on CD/DVD** to allow lifeIMAGE to automatically upload your CD (Microsoft Windows only) or click **Browse for exams** to select the location of exams yourself.

Step 2. lifeIMAGE detects exams and displays them to you. Confirm that these are the proper exams before uploading them. In the case of multiple exams, you can unselect any that are not relevant. Click **Next** and then **Upload** to proceed.

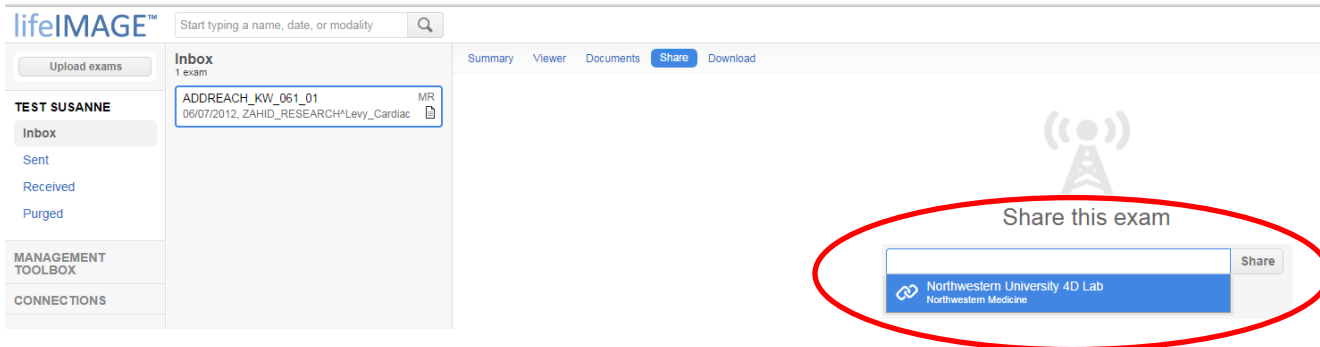
→ While exams are uploading, you will see a progress bar in the top left of the screen and in each exam you upload.



→ After a while you will see your uploading exam listed as 'pending' and once completed it will show it in the inbox:



- Once uploaded you now need to share the exam with NURAD4D, please do so by clicking on the exam. You will see a summary of the study on the right also showing the images as thumbnails. In the menu above the images you also see the **Share** button. You will see a box 'Start by typing a group or connection name', click in there and you will see Northwestern University 4D Lab popping up. Select this and push **Share**.



9. To complete the share you will need to fill out Exchange Details:

Summary Viewer Documents **Share** Download

Exchange Details

* = Required field

PROVIDE INFORMATION ABOUT THIS CASE

Notes:

PRIMARY CONTACT

* Admin Contact First Name:

* Admin Contact Last Name:

Admin Contact Phone:

* Admin Contact Email:

Admin Contact Title:

SECONDARY CONTACT

Clinical Contact First Name:

Clinical Contact Last Name:

Clinical Contact Phone:

Clinical Contact Email:

Clinical Contact Title:

AGREEMENT

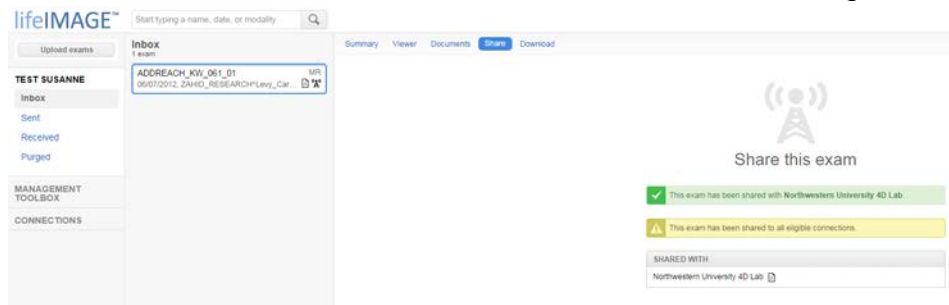
This is the first time you've shared with Northwestern Medicine Northwestern University 4D Lab. Please read and agree to their terms below.

At the request of Northwestern Medicine Northwestern University 4D Lab you are about to upload an imaging examination to a secure, cloud-based InBox for the continuing care and treatment of a shared patient. The imaging examination and

I agree to these terms

Cancel **Share**

10. After filling in all details and agreeing to the terms you have to push the **Share** button again. You will now see this screen to inform about successful image sharing:



11. The uploaded exams will stay 60 days in your Inbox. You need to share the images before that or else NURAD4D will not be able to receive them and you will need to go through the upload process again.

12. Once done with the data transfer, please logoff.

COMBINE Study CTI Safety Questionnaire

MRI MACHINES USE A VERY STRONG MAGNET TO GENERATE IMAGES. CERTAIN IMPLANTS, DEVICES OR OBJECTS MAY BE **HAZARDOUS** TO YOU AND/OR MAY INTERFERE WITH THE MR PROCEDURE. BEFORE ENTERING THE MRI ROOM YOU MUST **REMOVE ALL METALLIC OBJECTS.**

GFR VALUE > 60 _____ DATE _____

PLEASE INDICATE IF YOU HAVE ANY OF THE FOLLOWING:

<i>CARDIAC PACEMAKER</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<i>ARE YOU PREGNANT</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO
<i>IMPLANTED CARDIAC DEFIBRILLATOR (ICD)</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<i>ELECTRONIC DEVICE (DEEP BRAIN/SPINAL CORD/NERVE STIMULATOR)</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO
<i>INTERNAL ELECTRODES/WIRES</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<i>INJURED EYES WITH METAL FLAKES/SLIVERS/SHRAPNEL</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO
<i>ARE YOU CLAUSTROPHOBIC</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<i>EYELID SPRING OR WIRE</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO
<i>COCHLEAR IMPLANTS</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<i>MAGNETIC IMPLANTS</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO
<i>SWAN-GANZ OR THERMO-DILUTION CATHETERS</i>	<input type="checkbox"/> YES	<input type="checkbox"/> NO			
IF YES ANSWERED TO ANY OF THE ITALICIZED BOLD PRINT QUESTIONS SUBJECT IS NOT ELIGIBLE FOR MR					
BONE FUSION STIMULATOR	<input type="checkbox"/> YES	<input type="checkbox"/> NO	EAR SURGERY	<input type="checkbox"/> YES	<input type="checkbox"/> NO
TISSUE EXPANDER	<input type="checkbox"/> YES	<input type="checkbox"/> NO	HEAD SURGERY	<input type="checkbox"/> YES	<input type="checkbox"/> NO
EYE SURGERY	<input type="checkbox"/> YES	<input type="checkbox"/> NO	HEARING AID	<input type="checkbox"/> YES	<input type="checkbox"/> NO
HEART VALVE PROSTHESIS	<input type="checkbox"/> YES	<input type="checkbox"/> NO	TENS UNIT FOR PAIN	<input type="checkbox"/> YES	<input type="checkbox"/> NO
INSULIN OR DRUG INFUSION DEVICE	<input type="checkbox"/> YES	<input type="checkbox"/> NO	RADIATION SEEDS OR IMPLANTS	<input type="checkbox"/> YES	<input type="checkbox"/> NO
VASCULAR ACCESS PORT	<input type="checkbox"/> YES	<input type="checkbox"/> NO	WIRE MESH IMPLANTS	<input type="checkbox"/> YES	<input type="checkbox"/> NO
SHUNTS AND/OR STENTS	<input type="checkbox"/> YES	<input type="checkbox"/> NO	WORKED WITH METAL	<input type="checkbox"/> YES	<input type="checkbox"/> NO
BODY PIERCING JEWELRY	<input type="checkbox"/> YES	<input type="checkbox"/> NO	VASCULAR SURGERY	<input type="checkbox"/> YES	<input type="checkbox"/> NO
ANEURYSM CLIP (S)	<input type="checkbox"/> YES	<input type="checkbox"/> NO	IUD/DIAPHRAGM/PESSARY	<input type="checkbox"/> YES	<input type="checkbox"/> NO
BONE/JOINT PIN, SCREWS, PLATE etc...	<input type="checkbox"/> YES	<input type="checkbox"/> NO	TATOO/PERMANENT MAKE UP	<input type="checkbox"/> YES	<input type="checkbox"/> NO
OTHER FOREIGN BODIES OR IMPLANTS	<input type="checkbox"/> YES	<input type="checkbox"/> NO	JOINT REPLACEMENT OR PROSTHETIC IMPLANTS	<input type="checkbox"/> YES	<input type="checkbox"/> NO
SURGICAL STAPLES OR CLIPS	<input type="checkbox"/> YES	<input type="checkbox"/> NO	DENTURES OR PARTIALS	<input type="checkbox"/> YES	<input type="checkbox"/> NO
MEDICATION OR NICOTINE PATCH	<input type="checkbox"/> YES	<input type="checkbox"/> NO	DO YOU HAVE KIDNEY DISEASE	<input type="checkbox"/> YES	<input type="checkbox"/> NO
DO YOU HAVE ASTHMA OR OTHER RESPIRATORY DISEASE	<input type="checkbox"/> YES	<input type="checkbox"/> NO	ARE YOU ALLERGIC TO ANY DRUGS, MRI OR CT CONTRAST	<input type="checkbox"/> YES	<input type="checkbox"/> NO
DO YOU HAVE SICKLE CELL ANEMIA	<input type="checkbox"/> YES	<input type="checkbox"/> NO	HAVE YOU EVER HAD AN ALLERGIC REACTION	<input type="checkbox"/> YES	<input type="checkbox"/> NO

IF YOU HAVE ANSWERED YES TO ANY OF THE ABOVE PLEASE EXPLAIN: _____

SUBJECT'S NAME _____ SIGNATURE _____
(PLEASE PRINT)

BIRTHDATE _____ WEIGHT _____ HEIGHT _____ DATE _____

ID _____ Alpha Code ____ Date Questionnaire Completed ____/____/____

Staff member who interviewed the patient _____

COMBINE Protocol
MRI APPOINTMENT REMINDER AND INSTRUCTIONS

For: _____

- ❖ **Your next *COMBINE* MRI procedure** is scheduled for _____ at _____.
Plan on a time period of approximately 1.5 hours. Come to the clinic at Olson Pavilion, 710 North Fairbanks, Basement Chicago, IL.
If you cannot make this appointment, please call _____ at _____.

PLEASE DO THE FOLLOWING BEFORE YOUR CLINIC VISIT:

- Fasting for **4 hours prior** to MRI visit. (For example, if your appointment is at 8am, your last meal should be at 4am the same morning).
- If you take insulin, on day of the test take **one half** of your morning dose of **insulin**.
- DO NOT** take your Furosemide (Lasix) **treatment** dose the morning of the MRI (for individuals on Furosemide).
- DO NOT** take non-steroidal anti-inflammatory medications (Motrin, Advil, Ibuprofen, Naproxen) for 3 days prior to the MRI visit.
- We will review your blood pressure medications (ACE inhibitor or ARB) with you because certain blood pressure medications should be taken after the MRI test.
- Eat a snack after completing the MRI test

CHAPTER 57: COMBINE SPECIMENS FOR NIDDK REPOSITORY

57.1 Background

Participants who are enrolled in the CKD COMBINE Study will be invited to volunteer to provide biological samples to be stored for use in possible future studies. Consent language specific to repository samples collection can be found as part of the main consent form. (Note: NIH approval is required for Repository Consents before specimens can be taken out of the Repository). Template consent forms can be reviewed at the CKD website: http://qhsapps.ccf.org/ckdp/open_webdocs/Consent_Templates/Consent_Templates_TOC.htm Among those participants who consent for storage of biological specimens, serum, plasma and 24-hour urine samples will be collected at various time points as identified in the table below. Samples from COMBINE sites will be shipped to the NIDDK Biosample Repository at Fisher BioServices, Germantown, Maryland.

Contact information can be found in the CKD COMBINE Address Directory. For general questions and biosample shipment notification, use bio-niddkrepository@thermofisher.com.

57.2 Schedule, Type and Volume of Samples

COMBINE Samples Collected for NIDDK Repository

Specimen Type	COMBINE Collection Periods				
	B1	B2	F3	F6	F12
Serum - (gold top tube)	1 x 4.0 ml	1 x 4.0 ml	1 x 4.0 ml	1 x 4.0 ml	1 x 4.0 ml
Plasma – (light green top tube)	1 x 4.5 ml	1 x 4.5 ml	1 x 4.5 ml	1 x 4.5 ml	1 x 4.5 ml
24-hr Urine Collection	>20 ml	>20 ml	>20 ml	>20 ml	>20 ml

57.3 Training Requirements for Personnel Sending Samples

Each person shipping diagnostic specimens should be trained according to DOT and IATA regulations. Someone at each COMBINE site will be responsible for training the appropriate personnel.

No sample test kit submission is required for the COMBINE Study.

57.4 Logistics for Biosample Repository

Overview: The BioRepository will provide sample collection kits including the necessary blood collection tubes, packing and shipping materials, and Federal Express labels for collection and shipping of the samples. The sample collection kits will be shipped to the sites by Fisher. The tube labels to be used with all repository specimens will be supplied to the sites by the DCC with detailed completion instructions provided. The tube labels include pre-printed 3-digit identification numbers, in which the first 3 digits designate the NIDDK

BioRepository Site Identification code; the study team member will write in the CKD COMBINE Participants' ID in the final 6 spaces on the label. The labels will also include two spaces in which the study staff should mark the participant's CKD COMBINE alpha code, which will be used as an alternative ID by Fisher BioServices. Circle the appropriate type of specimen (plasma/serum). Tubes should be labeled immediately prior to when blood is drawn from the patient.

Follow the procedure identified in Section 57._ for specific sample processing information.

For consenting participants, study staff will fill one serum shipping tube (SST tube) and one plasma shipping tube (PST tube) and then store them in a refrigerator at +4 degrees Centigrade that is roughly equivalent to 39 degrees Fahrenheit. They should be shipped refrigerated and sent the day of collection (or if necessary, refrigerate overnight for shipping the next day) to Fisher BioServices using the shipping kits and packing materials provided by Fisher.

A completed paper copy of the Biorepository Serum and Plasma Mailing Form (Form # 300) should also be included in the kit shipped to Fisher. The information on the form must also be entered in the database.

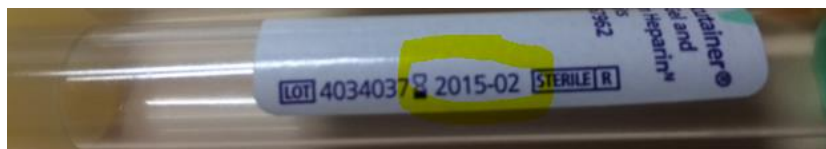
On arrival at the BioRepository, a Fisher BioServices staff member will divide the samples into aliquots according to the table below. Barcodes will be placed on each cryovials and entered in the repository database. Cryovials will then be placed in -70° C freezer for future ancillary studies.

Sample Type	0.2 ml Aliquots	0.5 ml Aliquots	1.0 ml Aliquots	5.0 ml Aliquots
Serum – 4.0 ml tube	qty. 10	(remainder of tube)	--	--
Plasma tube – 4.5 ml tube	qty.10	(remainder of tube)	--	--
24-hr urine >20 ml urine cup	--	--	qty.10	qty. 2 (remainder is discarded)

57.5 Fisher BioServices Repository Procedure Instructions

Blood

1. Be sure that the vacutainer tubes have not expired. Check that the date shown to the right of the hourglass on the BD label is equal to or later than the current month.



- In preparation for collecting the serum/plasma: complete and attach the participant I.D. labels provided by the DCC to the blood samples immediately prior to collection. Use the labels provided and place them lengthwise on the tubes. DO NOT write the participant's name or any other personal identification information (e.g., SS#, DOB) on the tubes.

Sample label:

3 x x - _____ - _____
COMBINE: Serum Plasma
Collect Date: ____/____/_____

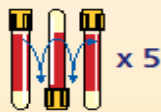
Note: The tube labels include pre-printed 3-digit identification numbers, in which the first 3 digits designate the NIDDK BioRepository Site Identification code; the study team member will write in the CKD COMBINE Participants' ID in the final 6 spaces on the label. The labels include two spaces in which the study staff should mark the participant's COMBINE alpha code, which will be used as an alternative ID by the BioServices Repository.

COMBINE Site	NIDDK BioSpecimens Site Number
George Washington Univ.	368
Northwestern Univ.	363
NorthShore Univ.	367
UCSD	364
Denver Nephrology	366
Univ. of Utah	365
Utah VA	354

- Collect the specimen in the appropriate and marked tube; either SST/PST vacutainer tube.
- After filling: (please see guides on Preparing A Quality Sample for serum and plasma on next pages as provided by the biorepository.)

How to Prepare a Quality Sample Using BD Vacutainer® SST™ Tubes

Invert
5
Times



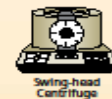
- Gently invert 5 times to mix clot activator with blood.

Clot
30
Minutes



- Allow blood to clot for a minimum of 30 minutes in a vertical position.
- Observe a dense clot.

Spin
10
Minutes



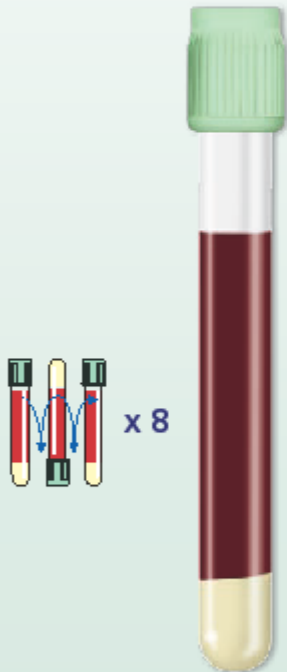
- Centrifuge at FULL SPEED (between 1100 and 1300g) for 10 minutes for swing-head units or 15 minutes for fixed angle units (balance tube in centrifuge).
- Barrier will form, separating serum specimen from dot.
- Transport spun tube to laboratory.



Helping all people
live healthy lives

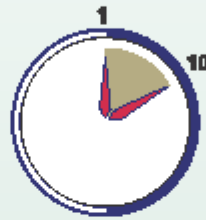
How to Prepare a Quality Sample Using BD Vacutainer® PST™ Tubes

Invert
8-10
Times

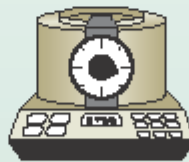


- Gently invert 8-10 times immediately after collection to mix lithium heparin anticoagulant with blood.
- Insufficient mixing may lead to microclot and fibrin strand formation.

Spin
10
Minutes



Centrifuge at
1100 - 1300g



- Centrifuge at full speed
1100 – 1300g for 13 mm Plus Plastic tubes
1000 – 1300g for 16 mm Plus Plastic tubes
for 10 minutes in a swing-bucket unit or
15 minutes for a fixed-angle unit
(balance tubes in centrifuge).
- Gel barrier will form to separate plasma from red blood cells.

Ready
for
Analysis



- Use in laboratory for plasma determinations in chemistry.

5. Then move the tubes to the refrigerator until the shipment is ready to be sent. Be sure that the refrigerator is securely closed.

6. Double check the subject ID, and verify that ID information on the vacutainer tubes matches that on the Form 300-Biorepository Serum and Plasma Mailing Form (Form # 300).
7. Date and identify the person completing the Form 300-Biorepository Serum and Plasma Mailing Form (Form # 300). Make a copy of each form; keep the copy and send the original with the shipment.
8. If more than one COMBINE participant's serum and plasma has been collected, then it is acceptable to ship both in the same shipper. Make sure each participant's samples are well-marked and placed in separate bags.

Urine

1. Be sure that the seal on the 90ml urine container has not been broken processing urine from the 24-hr collection in jug returned by participant (see Spectra MOP Chapter 43 for handling urine jug.)
2. Complete and attach the participant I.D. label provided by the DCC to the urine container immediately prior to collection. DO NOT write the participant's name or any other personal identification information (e.g., SS#, DOB) on the tubes.

Sample label:

3 x x - _ _ _ _ _ - _ _ _ COMBINE: 24-hr Urine Start Date: _ _ / _ _ / _ _ _ _

The urine container label includes a pre-printed 3-digit identification number, in which the first 3 digits designate the NIDDK BioRepository Site Identification code*; using a fine-tipped permanent marker (like a Sharpie), the study team member will write in the CKD COMBINE Participants' ID in the final 6 spaces on the label. The label also includes two spaces in which the study staff should mark the participant's CKD COMBINE alpha code, which will be used as an alternative ID by the BioServices Repository. The date 24-hour urine collection started on the space provided.

*Refer to page 57.3 for NIDDK Site repository numbers

3. Then move the urine container to the refrigerator until the shipment is ready to be sent. Be sure that the refrigerator is securely closed.
4. When preparing to ship, double check the subject ID, and verify that ID information on the urine container matches that on the Form 301-Biorepository 24-Hr Urine Mailing Form..
5. Date and identify the person completing the Form 301-Biorepository 24-Hr Urine Mailing Form.. Make a copy of each form; keep the copy and send the original with the shipment.
6. See next page for preparing sample shipments to Fisher.

Instructions For Shipping COMBINE Urine and Blood to the NIDDK BioSample Repository

1. Freeze the gel pack included in the shipping kit prior to sample collection.
2. Collect the urine in the specimen cup and screw the lid on the cup. Verify that the lid is secured tightly, and wipe any urine off the outside of the container.
3. Place the urine cup into the biohazard zip-lock bag with the absorbent sheet. Seal the bag. (Pic.1)
4. Insert the Vacutainers into the bubble wrap pouch (Pic.2). Place the pouch into the zip-lock bag with the absorbent sheet. Seal the bag. (Pic.3)
5. Place the frozen ice pack in the bottom of the foam cooler. (Pic.4)
6. Place the zip-lock bags containing the urine and Vacutainers on top of the gel pack. Make sure the urine container is in an upright position. Place additional bubble wrap or packing material inside the foam cooler to prevent the contents from shifting during shipment. (Pic.5 & 6)
7. Place the foam lid on the foam cooler. Place the Biorepository Mailing Forms on top of the foam lid. (Pic.7)
8. Close and seal the box with packing tape. Affix the "Exempt Human Specimen" label to the top of the box in the upper right corner. Affix the repository address label to the top of the box in the upper left corner. (Pic.8)
9. Use the pre-printed FedEx air bill to ship specimens to the NIDDK Repository:
 - a. Section 1, From: Fill in your name, return address, phone number and the date. Leave "Sender's FedEx Account Number" blank.
 - b. Section 2, Your Internal Billing Reference: Enter the study name "COMBINE".
 - c. Section 6, Special Handling: Place a check mark next to "No" under "Does this shipment contain dangerous goods?"
 - d. Section 7, Payment: Enter "1" under "Total Packages" and the total weight of the package under "Total Weight".
 - e. Follow the peel-and-stick instructions on the back of the preprinted air bill. As shown, affix the air bill to the side of the box.
10. If your organization does not have a regularly scheduled FedEx pickup, call Federal Express, 1-800-GO-FEDEX (1-800-463-3339). Tell them the account number (in Section 7, Payment) on the preprinted FedEx air bill and your pickup address. FedEx will dispatch a courier to pick up the package. Please schedule shipments Monday through Thursday. The repository is closed on weekends so do not ship specimens on Fridays. Specimens may be refrigerated and shipped on the following Monday.
11. Send a shipment notification to bio-niddkrepository@thermofisher.com on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number, study name and your contact information in the notification.
12. Contact the NIDDK Biosample Repository via email or call Heather Higgins (240-686-4703) or Sandra Ke (240-686-4702) regarding questions about packaging and shipping.



Pic.1



Pic.2



Pic.3



Pic.4



Pic.5



Pic.6



Pic.7



Pic.8

Revision date: 11 Nov 2014

000

FedEx Package
Express **US Airbill**

FedEx Tracking Number **8062 8133 3753**

Form No. **0215**

Sender's Copy

fedex.com 1.800.GoFedEx 1.800.463.3339

1 From Please print and press hard.

Date _____ Sender's FedEx Account Number **SENDER'S FEDEX ACCOUNT NUMBER ONLY**

Sender's Name _____ Phone (____) _____

Company _____

Address _____
Dept./Floor/Suite/Room _____

City _____ State _____ ZIP _____

2 Your Internal Billing Reference
Print 28 characters will appear on invoice. **0115214309**

3 To

Recipient's Name **HEATHER HIGGINS** Phone (____) **240 486-4706**

Company **FISHER BIOSERVICES, INC GOVT**

Address **20301 CENTURY BLVD**
Use correct dealer to PG, boxes or FID ZIP codes. Dept./Floor/Suite/Room _____

Address **BLDG. 6 Suite 400**
Use this line for the HOLD location address or in coordination of your shipping address.

City **GERMANTOWN** State **MD** ZIP **20874-9172**

Ship it. Track it. Pay for it. All online.
Go to fedex.com.

4 Express Package Service * In most locations. Packages up to 150 lbs. For packages over 150 lbs., use the new FedEx Express Freight 55 Airbill.

Next Business Day * Next business day. * Next business day. * Next business day.

FedEx First Overnight
Earliest next business morning delivery in select locations. Friday shipments will be delivered on Monday unless SATURDAY Delivery is selected.

FedEx Priority Overnight
Next business morning ** High-priority items will be delivered on Monday or Tuesday unless SATURDAY Delivery is selected.

FedEx Standard Overnight
Next business afternoon.
Saturday Delivery NOT available.

2 or 3 Business Days

FedEx 2Day A.M.
Second business morning.
Saturday Delivery NOT available.

FedEx 2Day
Second business afternoon.
Third business day delivery unless SATURDAY Delivery is selected.

FedEx Express Saver
Third business day.
Saturday Delivery NOT available.

5 Packaging * Declared value limit \$500.

FedEx Envelope* FedEx Pak* FedEx Box FedEx Tube Other

6 Special Handling and Delivery Signature Options

SATURDAY Delivery
SATURDAY Delivery. FedEx Standard Overnight, FedEx 2Day A.M., or FedEx Express Saver.

No Signature Required
Package may be left without signature in a signature for delivery.

Direct Signature
Someone at the party's address must sign for delivery. **Not applicable.**

Indirect Signature
If you are in business at recipient address, someone at a neighboring address may sign for delivery for residential deliveries only. **Not applicable.**

Does this shipment contain dangerous goods?

No Yes (as per assigned hazard classification) Yes (hazardous material not assigned) Dry Ice (Dry Ice 2, UN 1845) _____ to _____

Dangerous goods including dry ice may not be shipped in FedEx packaging or placed in a FedEx Special Service Box. Cargo Aircraft Only

7 Payment Bill to: _____ Enter FedEx Acct. No. or Credit Card No. below.

Sender (FedEx No. Sender's bill only) Recipient Third Party Credit Card Cash/Check

Swift Acct. No. **2820-0902-1** Exp. Date _____

Total Packages _____ Total Weight _____ Total Declared Value* _____

For liability is limited to \$500 unless you declare a higher value. See back for details. By accepting this bill you agree to the service conditions on the back of this Airbill and in the current FedEx Service Guide, including terms and conditions of liability.

Rev. June 2014 • Form 0215 (01/14) • ©1994-2014 FedEx • PRINTED IN U.S.A. 1215

PULL AND RETURN THIS COPY BEFORE AFFIXING TO THE PACKAGE. NO POUCH NEEDED.

NIDDK Biorepository Kit Re-Order Form COMBINE Study

Request Date: _____

Date needed by: _____

Study Coordinator: _____

Phone Contact #: _____

NIDDK Repository #: 3 _____

Shipping Address:

ITEM	UNITS	QUANTITY REQUESTED
Biorepository Kit	EACH	

Scan and email to: Bio-NIDDKRepository@thermofisher.com

or Fax supply re-order sheet to: 301-515-4049

--PLEASE ALLOW 7-10 BUSINESS DAYS FOR DELIVERY--

Each kit will contain the following items:

Qty	Biorepository Kit Item
1	90 ml sterile urine container with lid (for 24-hr urine sample)
1	4.0 ml SST vacutainer (gold top) tube (serum)
1	4.5 ml light green PST tube (lithium heparin additive) (plasma)
1	Bubble wrap sleeve (for tubes)
1	Bubble wrap (big cells)
2	Biohazard bags with absorbent material (urine and blood)
1	Label: 'Exempt Human Specimen'
1	Label: Fisher Bioservices return address
1	Label: Pre-printed Fedex Airbill
1	Freezer cold pack
1	Set of instructions for processing PST, SST tubes, and packing/shipping
1	Cardboard Box with styrofoam shipper

Endur-amide® Tablets – Sustained Release Niacinamide Tablets

Material Safety Data Sheet

Innovite Inc.
9914 SW Tigard Street
Tigard OR 97223
(503)-639-9562

Health: 1
Flammability: 1
Reactivity: 1

REVISION DATE : September 3, 2014

Endur-amide® Tablets

Page 1 of 5

Section 1 – Identification

MATERIAL

Vitamin Tablet

DOT CLASSIFICATION

Non-hazardous

CAS No. Not Established for tablets

DOT SHIPPING NAME

Not Regulated

FORMULA Proprietary Blend

DOT LABEL

None

CHEMICAL ID Vitamin Tablet

Section 2 – Composition and Ingredient Information

Ingredient(s)	Approximate Weight %	TWA/TLV
Niacinamide(CAS No. 98-92-0)	40%	None Established
Inert Tablet Binders (CAS not established)	60%	None Established

Section 3 – Hazards Identification

Chemicals listed as Carcinogens by:

Natl Toxicology Program - No
I.A.R.C. Monographs - No
OSHA - No

Stability: Stable Unstable Conditions to Avoid: None known

Hazardous Decomposition Products: None

Hazardous Polymerizations: Conditions to Avoid: None known
May Occur Will Not Occur

Incompatibility (Materials to Avoid)
Water other (strong oxidizing agents)

Material Safety Data Sheet

Innovite Inc.
9914 SW Tigard Street
Tigard OR 97223
(503)-639-9562

Endur-amide® Tablets

Page 2 of 5

Section 4 – First Aid Measures

Primary Routes of Entry – Skin Contact : X Eye Contact : X
Inhalation : X Ingestion :

Effects of Overexposure

No information available for human overexposure of this specific product. Based on available information from toxicity studies, it is anticipated that this material will not be toxic upon ingestion and will produce only mild irritation upon eye and skin contact.

Overexposure is low probability - No effects indicated

Eyes: Flush eye with water for several minutes. Seek medical attention if irritation develops.

Skin: Wash effected areas with water and soap if available for several minutes. Seek medical attention if irritation develops.

Ingestion: If swallowed give 3 to 4 glasses of water but DO NOT induce vomiting. If vomiting does occur, give fluids again. Get medical attention to determine whether vomiting or evacuation of stomach is necessary. Do not give anything by mouth to an unconscious or convulsing person.

Inhalation: Inhalation unlikely, remove from area to fresh air. Seek medical attention if discomfort or other symptoms develop.

Section 5 – Fire and Explosion Information

Flash Point: > 100°C (estimated)

Auto Ignition Temperature: Not known

Lower Explosion Limit (%): Not Applicable

Upper Explosion Limit (%): Not Applicable

Extinguishing Media: Foam X Alcohol Foam CO₂ X
Dry Chemical X Water X Other

Special Fire Fighting Procedures:

Evacuate personnel to safe area. Firefighters should wear protective clothing and use self-contained breathing equipment. Cool fire exposed containers with water spray, CO₂ or Foam.

Unusual Fire and Explosion Hazards:

Not applicable

Material Safety Data Sheet

Innovite Inc.
9914 SW Tigard Street
Tigard OR 97223
(503)-639-9562

Endur-amide® Tablets

Page 3 of 5

Section 6 – Accidental Release Information

Steps to be Taken in Case of Material Spill or Release

Carefully shovel spills into appropriate containers for disposal and place in compatible containers for disposal.

Waste Disposal Methods

Dispose of in compliance with all Federal State and local laws and regulations. Incineration is the preferred method.

Section 7 - Storage and Handling

Precautions for Storage and Handling:

No special precautionary health measures should be needed under anticipated use. Store in a dry place at or below room temperature. Avoid container exposure to heat or direct or intense sunlight.

Section 8 – Personal Protection Information

Engineering Controls

In processes where dust or airborne particulates may be generated, proper ventilation must be provided in accordance with good ventilation practices.

Respiratory Protection

In processes where dust or airborne particulates may be generated, a NIOSH/MSHA jointly approved respirator is advised in the absence of proper environmental controls.

Protective Gloves

Use good industrial hygiene practices to minimize skin contact. Rubber gloves are optional.

Eye Protection

Use good industrial hygiene practices to minimize eye contact.

Other Protective Equipment

Use good industrial hygiene practices

Material Safety Data Sheet

Innovite Inc.
9914 SW Tigard Street
Tigard OR 97223
(503)-639-9562

Endur-amide® Tablets

Page 5 of 5

Section 12 – Ecological Information

This material has not been tested for environmental effects. No negative effects expected.

Section 13 – Disposal Information

Discharge, treatment, or disposal may be subject to national, state or local laws.

Section 14 – Transportation Information

DOT CLASSIFICATION

Non-hazardous

DOT SHIPPING NAME

Not Regulated

DOT LABEL

None


Section 15 – Regulatory Information

No specific notes

Section 16 – Other Information

No specific notes

End of Document

 MATERIAL SAFETY DATA SHEET (ACCORDING TO 91/155/EC)	
Effective Date (DD/MM/YY):	27/AUG/08 <i>27 AUG 08</i>
Version No:	03
The current version of this MSDS is available from: Pharmaceutical Sciences, Shire Pharmaceutical Development, Hampshire International Business Park, Chineham, Basingstoke, Hampshire RG24 8EP, UK.	
1. IDENTIFICATION OF THE SUBSTANCE AND COMPANY UNDERTAKING THE MANUFACTURING OF THE SUBSTANCE	
Substance name (as on container labels):	Lanthanum Carbonate
Unique reference number(s):	SPD405
Company undertaking name & address:	Shire Pharmaceutical Development, Hampshire International Business Park, Chineham, Basingstoke, Hampshire, RG24 8EP
Telephone:	+44 1256 894000
Emergency telephone number:	CHEMTREC Within U.S. 1 800 424 9300; Outside U.S. +1 703 527 3887
2. COMPOSITION/INFORMATION ON INGREDIENTS	
Substance:	Lanthanum Carbonate
% Content:	100%
CAS Number:	54451-24-0
Classification:	Not available
EINECS:	Not available
3. HAZARDS IDENTIFICATION	
Most important hazards:	None
Specific hazards:	None
Lanthanum Carbonate is not classified as a dangerous substance under "The Chemicals (Hazard Information and Packaging for Supply) Regulations 2002".	
4. FIRST AID MEASURES	
Skin contact:	Wash with soap and water and rinse thoroughly with water.
Eye contact:	Open the eye and rinse with running water for several minutes. Consult a physician.
Ingestion:	Accidental ingestion of significant amount of Lanthanum Carbonate is unlikely but, if it occurs, rinse the mouth thoroughly with water and consult a physician. The following symptoms may occur: burning sensation in the mouth and throat, coughing, wheezing, laryngitis, shortness of breath,

Inhalation:	headache, nausea and vomiting. Supply fresh air. Apply artificial respiration if necessary. Keep the subject warm. Consult a physician if any symptoms persist.
5. FIRE FIGHTING MEASURES	
Suitable extinguishing media:	As appropriate to the surroundings. Lanthanum Carbonate is not combustible.
Unsuitable extinguishing media:	None
Special hazards in fire:	None
Required special protective equipment for fire fighters:	None
6. ACCIDENTAL RELEASE MEASURES	
Personal precautions:	Remove non-essential personnel from the area. Wear protective clothing to prevent skin contact and inhalation.
Environmental precautions:	Do not allow to enter the soil or drainage and sewage systems. If such contamination is suspected inform the relevant authorities.
Methods for cleaning:	Use mechanical methods and ensure adequate ventilation. Collect material in suitable containers for disposal in accordance with local regulations.
7. HANDLING AND STORAGE	
Handling:	Wear safety glasses and gloves.
Technical measures/precautions:	Local ventilation or dust extraction. Protect against electrostatic charges.
Storage:	Keep away from acids.
Technical measures/storage conditions:	Store in sealed containers in a cool, dry, well-ventilated place.
8. EXPOSURE CONTROLS/PERSONAL PROTECTION	
Engineering measures:	Control of dust.
Control Parameters:	None specified.
Personal protection equipment:	Face mask for breathing protection if large quantities are being handled and/or dust is generated.
Eye protection:	Safety glasses.
Hand protection:	Gloves.
Hygiene measures:	Basic precautions for handling chemicals. Avoid skin and eye contact. Wash hands during breaks and at the end of working. Do not eat or drink whilst working.
9. PHYSICAL AND CHEMICAL PROPERTIES	
Appearance:	White crystalline powder
Odour:	None
pH:	Not applicable

Boiling point:	Not applicable
Melting point:	Not applicable
Flashpoint:	Not applicable
Explosive properties:	Not applicable
Vapour pressure:	Not applicable
Relative density:	Not applicable
Solubility:	Insoluble in water
Oxidizing property:	Not applicable
Flammability:	Not combustible
Partition Coefficient:	Not applicable
10. STABILITY AND REACTIVITY	
Conditions to avoid:	None known
Materials to avoid:	Strong acids. Reaction produces carbon dioxide
Hazardous decomposition products:	Carbon dioxide
11. TOXICOLOGICAL INFORMATION	
Pharmacology: Lanthanum carbonate is a rare earth metal that acts in the lumen of the gastrointestinal tract to bind dietary phosphate.	
Acute toxicity Oral: No significant effects following oral administration to mice, rats and dogs at a limit dose of 2000mg (salt)/kg. IV: Intravenous maximum non-lethal doses were 3 and 6.25mg (chloride salt)/kg in mice and rats respectively; there were no clinical signs at these doses. Despite potential for interference with calcium metabolism, no significant systemic effects in general pharmacology studies, probably due to poor absorption.	
Repeat dose toxicity: Lanthanum carbonate at oral doses of up to 2000mg (salt)/kg/day was well tolerated in studies of up to 6 months in rats and 12 months in dogs.	
Irritation: Skin: May cause irritation Eye: May cause irritation, reddening and blurring.	
Sensitisation: May cause sensitisation in sensitive subjects. Prolonged skin exposure may cause dermatitis.	

Genetic toxicity:
No evidence of genotoxicity in a standard battery of tests.

Carcinogenicity:
Not carcinogenic in mice or rats. An increased incidence of benign adenomas in the glandular region of the stomach in male mice at 1500mg (salt)/kg/day was considered not relevant for human exposure.

Reproductive effects:
No effects upon fertility or foetal survival, growth and development in the rat. Increased pre- and post-implantation loss, reduced foetal weight and delayed skeletal ossification in rabbits as a consequence of maternal toxicity.

Other adverse effects:
None known.

12. ECOLOGICAL INFORMATION

Environmental risk considered negligible.

13. DISPOSAL CONSIDERATIONS

Dispose in accordance with local regulations.

14. TRANSPORT INFORMATION

Classification data: No special packaging considerations. Do not transport with strong acids.

15. REGULATORY INFORMATION

Lanthanum Carbonate is not classified as a dangerous substance under EU regulations.

16. OTHER INFORMATION

Recommendations/restrictions:
This Material Safety Data Sheet incorporates information provided by the manufacturer.

RD-701-SF-001 (January 2007)



Date: August 22, 2014

CERTIFICATE OF ANALYSIS

List No: 169P (placebo)
Lot No: 081405
Product: PLACEBO

	<u>Specifications</u>	<u>Found</u>
Physical Appearance:	Mottled, Off-White Tablet, EFC	CONFORMS
Tablet Size:	0.365" x 0.770" Oval	CONFORMS
Tablet Thickness:	0.295" ± 5%	0.300"
Weight Variation:	USP 35 ± 5%	CONFORMS
Actual Tablet Weight:	1124 mg
Dissolution:		CONFORMS

Exp. Date: AUGUST 2019

Mfg Date: AUGUST 22, 2014

Made in USA

INGREDIENT STATEMENT:

Cellulose, Vegetable Waxes (Rice Bran and/or Carnauba), Stearic Acid (Veg), Magnesium Stearate (Veg), Silica.

