LONGITUDINAL ASSESSMENT OF BARIATRIC SURGERY (LABS)

Ancillary Studies Guidelines

The LABS Steering Committee will evaluate protocols that enhance the ability of LABS: [1] to document the efficacy and complications of bariatric surgery and its role in the overall management of obesity; and [2] to address other important questions related both to clinical aspects of obesity and its co-morbidities and underlying mechanistic and other basic science issues.

Definition of studies ancillary to LABS

Ancillary studies propose questions and test hypotheses that are relevant to the goals and purposes of LABS but are not addressed by LABS-funded core or sub-study protocols. An ancillary study, by definition, derives its financial support from sources other than the funds awarded by NIDDK for support of the LABS consortium. While ancillary studies will generally utilize information about, or specimens obtained from, patients already enrolled in the LABS core database, they may involve additional study sites, investigators, specimen or data collection, procedures, patients, or other treatments. By contrast, sub-studies are projects conducted by LABS investigators at participating LABS sites with costs that are covered by the funds allocated to LABS.

The LABS consortium will collect a large and uniquely well-characterized sample of obese people and will follow them through, and after, one of several kinds of bariatric surgery. To make the best possible use of this extraordinary resource, LABS encourages investigators to develop ancillary studies in conjunction with the consortium and to involve other investigators, within and outside of LABS, in this process. Each ancillary study *must* include at least one LABS Principal Investigator or Co-investigator and must have the approval of the Principal Investigator at each LABS Clinical Center site proposed to participate in the ancillary study protocol.

The LABS Steering Committee must evaluate and approve or disapprove all ancillary studies and ensure that the ancillary studies do not impose an unacceptable burden on LABS staff or participating patients or conflict with the aims of LABS. Data collection for funded ancillary studies may not proceed without the approval of the Steering Committee.

Submission of an Ancillary Studies Proposal

All ancillary studies proposals must be submitted through the LABS Data Coordinating Center (DCC) to:

Frani Averbach
University of Pittsburgh
Epidemiology Data Center
127 Parran Hall
130 DeSoto Street
Pittsburgh, PA 15261

Telephone: (412) 624-3773
FAX: (412) 624-5268
E-mail: Averbachf@edc.pitt.edu

The current submission process, described below, was revised in November 2008 based on experience with two prior cycles of applications and because of the recognized need to conduct peer-review evaluations of ancillary studies that will not undergo NIH peer-review. Potential applicants should, therefore, follow the current guidelines in preparing and submitting applications.

Timing of Submissions: *Proposals that will be submitted to the National Institutes of Health (NIH) for funding should be submitted to the LABS SC no less than 3 months prior to the NIH submission date to assure that LABS approval can be secured in time to dovetail with the NIH process.* LABS will make every effort to complete review of such within 4-6 weeks, allowing successful applicants 6-8 weeks to prepare and submit applications for funding. Note that detailed scientific reviews of such proposed ancillary studies will be conducted by the NIH Study Sections.

RFA DK-03-022, which established the initial Ancillary Studies Program related to LABS, has expired. However, applications for support of Ancillary Studies may still be submitted to NIH (see standard deadlines at: (http://grants2.nih.gov/grants/funding/submissionschedule.htm). There is also a program announcement (PAR-07-024) titles "Ancillary Studies to Major Ongoing NIDDK and NHLBI Clinical Research Studies (R01)" which solicits grant applications from qualified investigators to conduct ancillary studies with ongoing clinical research studies such as LABS (http://grants.nih.gov/grants/guide/pa-files/PAR-07-024.html). Deadlines for the various steps in the evaluation process for Ancillary Studies that are intended for submission to NIH under any of the above sets of deadlines are indicated in Table 1.

Ancillary studies that will seek funding from a source other than NIH should be submitted to LABS for its approval *at least six months prior to the intended project starting date*, allowing LABS to conduct its own evaluation. See the additional guidelines for submission of ancillary studies that will not under go NIH peer review (Appendix A).

Table 1: LABS Ancillary Study Applications: Timeline Related to NIH Submission Deadlines

Ancillary Applicant Action Item	Time Prior to NIH Submission Deadline
3-page preliminary proposal to DCC	3 months
Proposal PI must contact DCC if DCC data management and analytical support required by:	2 months
Proposals to DCC for minimal budget analysis or for those who want LABS data only	6 weeks
Completed proposals to DCC. For distribution to Clinical Centers for burden analysis and to SC to confirm conformity with approved 3 page proposal	4 weeks
NIH R01 submission deadline	

Upon submission, send a complete copy of the submitted proposal to the DCC (see address above).

The Proposal

Proposals for all ancillary studies must be submitted to the DCC for review by the SC. *A cover letter of no more than one page should indicate why the proposed study should be conducted as an ancillary study to LABS rather than as a separate and independent project.*

Proposals should be concise, but contain sufficient detail to allow a thorough assessment of the relevance of the proposal to the goals of LABS, its scientific importance and possible impact on patient recruitment and follow-up, as well as any added workload for LABS staff. We expect that typical proposals will be approximately 3 pages in length, single spaced in an easily readable type font on 8½ x 11 inch paper with one inch margins on all sides. The components of the proposal should include:

[1] Project Title;

[2] List of Principal and Co-Investigators by name and institution;

[3] Clear statement of the hypotheses to be tested;

[4] An abstract section including (a) Background, (b) Specific Aims; (c) Outline of the protocol, clearly indicating procedures to be performed on and samples to be collected from patients, (d) List and brief description of any non-routine analytical methods employed; and (e) Informative reference citations.

[5] Number(s) of patients required, with statistical justification including sample size and power calculations;

[6] List of LABS sites contributing patients, and any other collaborating LABS or non-LABS sites. Close collaboration with the participating LABS sites through the entire process is highly encouraged. *The proposal must be accompanied by letters from the PIs of all collaborating LABS Clinical Centers and any other collaborating scientists indicating their roles in the project and their willingness to participate.* Once funding decisions are made, participating LABS sites must once again confirm their participation in the proposal and if participation is not possible at that time, another willing LABS site may be substituted with the consent of the LABS Steering Committee.

[7] Indication of numbers and sizes or amounts of biological samples required, and other data elements to be collected, including data required from the LABS core database;

[8] LABS parent study and participant burden: Describe the impact of the study on LABS recruitment and retention. Provide details on the time and effort required of participants and burden on clinical centers.

[9] Projected costs/budget: The proposed budget and intended funding source for project. Provide evidence that the proposed budget will be sufficient to complete the project.

Ancillary Study Review Process

Review Criteria: The SC will give priority to studies which: (1) contribute to LABS' aim of examining a broad range of relevant research questions; (2) make important use of the unique LABS patient cohort; (3) do not interfere with or duplicate the main LABS objectives or those of other accepted ancillary studies; (4) produce minimal burden on LABS participants and minimal demand on LABS resources, such as blood samples and tissues, that are also required for accomplishing the goals of the major LABS protocols; (5) have valid scientific merit; and (6)

could not readily be accomplished as separate projects independent of LABS. It is a goal of LABS to facilitate as many high-quality ancillary proposals as possible.

Initial Evaluation: The SC will review proposals on an on-going basis LABS will not carry out an in-depth scientific review of proposals that will be undergoing significant scientific scrutiny via a peer review process (e.g. NIH study section). The review will focus on the feasibility, overlap with LABS projects, and study/participant burden. A LABS Clinical Center coordinator will review the feasibility of the proposed study in relationship to LABS resources. Proposals will initially be categorized by the ASC into five groups, in order of decreasing interest to LABS:

1) The ancillary study's aims are fully consistent with the overall goals of LABS, while distinct from those being addressed by the major LABS aims or protocols. The proposed study makes unique and valuable use of LABS assets including patients, may involve collecting novel samples, and may also use data or samples collected for the main LABS studies.

2) The ancillary study's aims supplement those addressed by the major LABS aims or protocols. They may utilize data from the core database, may involve collection of at least some novel data not collected for the major LABS protocols, and may utilize specimens collected for major LABS protocols (e.g. blood samples, or tissues) for novel analyses.

3) The ancillary study's aims are already addressed to some degree within the LABS main or sub-study aims or protocols. Such studies are unlikely to be approved unless the overlap with main or sub-study protocols is minimal.

4) The ancillary study's aims are outside the interests of LABS.

5) The ancillary study's aims could be met by an independent project, and do not require an affiliation with LABS.

6) Irrespective of the relevance of the study's aims, an ancillary study that makes unacceptable demands on LABS patients, staff, or on the pools of available biological samples..

Scientific Review: Proposals in categories 1 and 2, and possibly some in category 3 that will be submitted to the NIH will include a preliminary review of scientific merit, but will focus on the feasibility of the study for LABS and an assessment of overlap or interference of work already being completed in LABS. This review is not meant to provide extensive scientific feedback to applicants. The latter will be obtained as a result of the detailed scientific review occurring through the NIH peer review system.

For other proposals including industry-sponsored ancillary studies, if no other acceptable peer review has taken, or will take place, the Steering Committee, will conduct ascientific review of a proposal. If the Steering Committee lacks expertise on the subject of a proposal, an external reviewer will be identified to conduct the review. This review process is outlined in Appendix A of the guidelines.

During review, ancillary studies proposals will be circulated to the PIs of the LABS Clinical Centers for comment. Interested LABS investigators may contact the PI of the proposed ancillary study and request participation as collaborators in the study. In addition, as appropriate, the SC may recommend that the ancillary PI consider adding additional sites to provide added statistical power, a more diverse population, or to contribute specific expertise. The LABS Data and Safety Monitoring Board (DSMB) may also be asked to judge the demands the proposed study places on participants and the priority in relation to LABS objectives.

The ASC will determine whether an ancillary study should be given approval. This recommendation will be based, in part, on whether the ancillary study interferes with the LABS protocols and whether it competes with other proposed ancillary studies for participant or staff time and/or biological resources (e.g. blood, tissues). To maximize efficient use of patients and other resources, the SC may recommend that several similar and potentially competing ancillary study proposals be combined. The Steering Committee will determine which ancillary study will receive final approval if several meritorious proposals compete for the same LABS resources.

When studies request specimens, these requests will be evaluated in terms of (1) the specific need for LABS specimens (2) the totality of requests made for the specimens.(see Studies Proposing to Use Stored LABS Specimens , below).

Conditional Approval: If the SC determines that a proposal contains elements that, if adjusted, would allow for approval, it will be given conditional approval and the PI will be notified with a list of changes to be made to gain SC approval.

Protocol Changes: Applicant PIs must notify the SC through the LABS project coordinator no less than 4 weeks before the submission deadline of the proposals of any substantial changes from the approved 3 page application that appear in the final proposal. This applies whether the changes are investigator initiated or are made due to recommendations from a review group such as the ASC. Substantial changes include, but are not limited to, change of sites, PIs, endpoints, hypotheses, biospecimens or data items, major changes in sample sizes, and merging of applications. These modifications must be conveyed to the LABS coordinator electronically highlighting modified sections.

In all instances of substantially altered applications, the SC will re-evaluate whether the modified project still merits SC support as a LABS-approved Ancillary Study. LABS will compare all final applications with approved, preliminary 3-page applications. SC approval for submission will be withdrawn from any applications that contain appreciable but previously undisclosed modifications at that time.

After a study is approved, significant protocol changes must be reported to and approved by the LABS SC. Failure to do so, may lead to the withdrawal of LABS support.

Studies Proposing to Use Stored LABS Specimens: Initial Steering Committee approval for an ancillary study to use stored LABS specimens will be contingent upon the availability of the requested specimen beyond the needs of core LABS protocols and approved ancillary studies already underway. An additional consideration for such studies is the importance and uniqueness of the study, should its approval and subsequent use of the specimens deplete the stored supply. For more information on apply to use stored specimens, refer to Appendix B: Policy for Non Renewable Sample Requests from LABS.

Failure to obtain funding: If, within 8 months of initial approval by the Steering Committee, an investigator is unsuccessful in obtaining the necessary resources to conduct a study that would deplete the required biospecimens, the initial Steering Committee approval of the project will generally be withdrawn and the Steering Committee will consider other proposals to use these specimens. Investigators are required to inform the Data Coordinating Center (DCC) of funding decisions within 5 working days of their receipt, and if unsuccessful, whether a revised application is planned. In the latter case, a revised proposal accompanied by the scientific critique of the initial funding application must be submitted to the DCC within the following 60 days for reconsideration. If the SC approves the revised application, the SC *may* keep the required specimens or other resources available for the project for a further 8 months, allowing time for submitting a revised application. However, the Steering Committee reserves the right to

reallocate these LABS resources for another approved project. In the absence of a revised application, the initial approval for the project will be withdrawn.

Conflict of Interest: If any SC member proposes an ancillary study, collaborates with an investigator who proposes an ancillary study, or is affiliated with the institution of an investigator who proposes an ancillary study, he or she will be recused from considering that proposal, similar to NIH peer review policies for avoidance of actual or perceived conflicts of interest.

Duration of Initial SC Approval Initial LABS approval of any application received after March 1, 2005 is considered for only one application for funding, with a date to be stipulated in the application and resulting LABS approval statement. Investigators submitting a revised application must renew their LABS approval by submitting a new 3-page proposal to LABS in accordance with the schedule indicated in Table 1.

Final Steering Committee Approval

TheSteering Committee will consider several additional issues before granting *final* approval to conduct an ancillary study.

IRB Approval: All ancillary studies must receive necessary approvals from IRBs at the institutions involved. Documentation of IRB approval must be submitted to the LABS DCC before an ancillary study can be initiated in conjunction with LABS.

Confidentiality: Confidentiality of individually identifiable data about LABS participants must be assured. LABS provides no assurances that ancillary study investigators will be able to identify and contact participants in the future.

Availability of Funding: For ancillary study applications to NIH or other organizations for funding, *initial approval* by the Steering Committee constitutes approval to apply for such funding. *Final approval* requires submission by the ancillary study PI to the DCC of documents establishing a definite commitment for funding. However, because several applications that compete for LABS resources may receive funding, receipt of such funding does not guarantee final SC approval. In these circumstances the SC would work with the relevant PIs to find compromises that would allow the funded applications to proceed in way that would not place an unacceptable burden on labs patients or other resources prior to awarding of final SC approval. *No data collection or use of LABS patients, data or other resources may begin without final approval from the Steering Committee.*

Ancillary Studies must Provide Funding for Hidden Costs: In assessing the acceptability of an ancillary study proposal, the Steering Committee will be concerned with both the explicit and the hidden costs to LABS entailed by the proposal (e.g., burden or other costs to the DCC for additional data collection and statistical support, burden or other costs to Clinical Centers for sample collection and shipping, burden or other costs to LABS participants). The ancillary study's PI should provide evidence that adequate support for carrying out all functions required for the ancillary study will be available and that the ancillary study will not add any additional, unfunded cost to LABS.

Agreement to Provide Severe Adverse Events Reports: Ancillary study applicants must agree to submit to LABS Severe Adverse Events (SAE) Reports that may be required by the LABS Steering Committee or Data and Safety Monitoring Board. These reports are in addition to any SAE reports required by the IRBs of institutions participating in the ancillary study.

Post Funding Confirmation of LABS Sites' Participation: Prior to final Steering Committee approval of a funded proposal, each LABS site that is participating must reaffirm their interest and ability to participate in the study. If a LABS site cannot participate, another willing LABS site may be substituted with the consent of the LABS Steering Committee.

Data Issues

The release of any LABS data from the DCC to an ancillary study investigator is subject to the rules and timeline regarding release and use of data defined in the LABS Publications and Presentations Policy. In addition, the use of LABS data for purposes other than the stated aims of the ancillary study, including the use of LABS data as a part of another publication, grant application or any other previously unapproved use of the data must be reviewed and approved by the Steering Committee.

In general, *all* data collected by the ancillary study must be provided to the LABS DCC electronically and in timely fashion for integrating into the main database and, ultimately, archived with the other LABS data. In return, ancillary study investigators will receive an analysis file containing both their data and approved LABS data. The ancillary study PI will be given the first opportunity to analyze, present, and publish data collected for the specific aims of the ancillary study. After a reasonable time (in general, 18 months after the ancillary study PI has received the cleaned data), the ancillary study data will be made available for additional uses by LABS investigators, in collaboration with the ancillary study investigators. It is the responsibility of the ancillary study PI to state to the Steering Committee in writing in advance of beginning the study any special circumstances that would make these guidelines for data sharing impossible or undesirable. Reasonable and justified requests for limiting Steering Committee access to the data will be considered. In addition, the acquisition or analysis of specialized data sets, such as high-throughput genotyping or microarray data, by the DCC may be negotiated between the PI of the ancillary study and the DCC prior to granting by the Steering Committee of final permission to proceed with the study.

Additional samples collected for the ancillary study and available for archiving will also become part of the LABS archive.

Additional Data Requests for Funded Ancillaries: Funded ancillary studies seeking to receive data from the main LABS study which were not requested in the original proposal must submit a written request. The request must include a precise description of the data requested, a justification for the receipt of such data, an explanation of the use and preliminary plans for analyzing and reporting the additional data. The ancillary study PI is responsible for working with the DCC to determine any impact that the additional data might have on DCC operations, and for covering the costs incurred by the DCC in providing the requested data. The ASC will review the proposal to determine whether or not it should be recommended to the Steering Committee for final approval.

Renewal Requests for Funded Ancillaries: Funded ancillary studies seeking to obtain a renewal for their grant should notify the DCC. If the science of the ancillary remains the same and the only request is for longer follow-up, it will be reviewed in an expedited fashion. If the specific aims of the study change or the protocol is fundamentally altered, the new proposal will have to go through the review process for new studies. Changes will need to be detailed in brief summary format along with scientific justification (3 pages or less) and submitted to the DCC along with a copy of the original study protocol. The DCC will review the changes to determine if additional resources will be required. The proposed study will undergo SC review.

Non-NIH sponsored Ancillary Studies

Proposals for ancillary studies that will seek funding from sources other than NIH will be evaluated in accordance with the procedures described above. It is the responsibility of the PI to obtain agreement from the sponsor through an appropriate contractual mechanism that all data will be provided to LABS to combine with LABS data . Study conduct must comply with all existing LABS, individual institutions within LABS, and NIH policies and guidelines. Specifically, the sponsor may not interfere with analysis or publication of any data obtained during the course of an ancillary study to LABS. Involvement of a study with industry may require a Cooperative Research and Development Agreement (CRADA).

Publications and Presentations

Proposals for all abstracts, presentations, and publications from an ancillary study must be submitted for review and approval by the LABS Publications and Presentations Committee prior to submission or presentation, in accordance with the LABS rules for publications and presentations.

Each manuscript and abstract is generally expected to include a LABS investigator as co-author, except under circumstances that should be stated and justified as part of the original submission to the ASC.

All publications, presentations, and abstracts derived from an approved ancillary study must acknowledge support from the LABS Consortium grants as well as the specific support for the ancillary study.

Acknowledgment In drafting these guidelines, the LABS ASC had the benefit of ancillary studies guidelines developed previously for other NIH-funded research consortia. Specifically, both concepts and, in some instances, specific language were borrowed from ancillary studies policies developed for the NIDDK and NHLBI-sponsored Virahep-C project, the LOOK Ahead and Halt C Trials, and the NASH CRN.

Appendix A: Guidelines for Ancillary Studies that will not Undergo NIH Peer Review

This policy describes the guidelines and procedures applicable to LABS ancillary study proposals that will not be reviewed by an NIH Study Section. In such situations, the Steering Committee will conduct its own scientific review of the proposal. If the Steering Committee lacks expertise on a particular subject, external reviewers may be identified. Application submission guidelines and review procedures are outlined below.

A. General Guidelines

Ancillary study proposals submitted for scientific review should be easily read and understood by individuals who may not be experts in the scientific area of research, but who are sufficiently knowledgeable in scientific areas related to the research to be able to evaluate the proposal fairly. These ancillary study proposals should contain sufficient detail to allow adequate scientific review and assessment of the relevance of the proposal to the LABS study, as it impacts recruitment, follow-up, biospecimen inventory and workload. The conceptual or clinical framework, design, methods, and analytical procedures should be adequately developed, well integrated, well reasoned, and appropriate for the aims of the project.

B. Application Format:

Each application should include:

1. List of all investigators, their proposed role in the study, and their biographical sketches (limited to 2 pages each).
2. Description of the resources and environment for conducting the study ($\leq$ 1 page).

Items 4-9 below should be no more than 15 pages in length using Times New Roman Font 10

3. Introduction
   This section should provide background information with pertinent key references. It should also clearly outline the significance of the research question and how the outcome(s) of the study will advance scientific knowledge and/or clinical practice. The introduction must indicate why the LABS consortium is necessary to perform the proposed work.
4. Hypotheses and specific aims
5. Research design
   This section should describe the overall research design and implementation plan. It should also clearly delineate the activities/role(s) required of LABS personnel, central laboratory, repositories, data coordinating center, and other relevant parties and facilities. A timeline (including anticipated start date, enrollment period [if applicable], sample collection period [if applicable], and analysis period at a minimum) should be provided.
6. Methods
   This section should provide a concise description of the methods to be employed. The feasibility and limitations of the project should also be addressed.
7. Data analysis
   At a minimum, this section should include a power analysis and a description of the analytical plan. It should also identify any limitations inherent within the analytical plan.
8. Risk and Safety concerns

Describe the potential risks to subjects (physical, psychological, social, legal, or other) and assess their likelihood and seriousness.
Describe the planned procedures for protecting against, or minimizing, potential risks, including risks to confidentiality, and assess their likely effectiveness.
Describe the potential benefits of the research to the subjects and others. Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.
Discuss the importance of the knowledge to be gained as a result of the proposed research. Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result. Include an Informed Consent document (draft only, IRB approval not required), if applicable, as well as a Data and Safety Monitoring Plan (for more information on how to create one, please see: http://www2.niddk.nih.gov/Research/ClinicalResearch/ClinicalResearchDataandSafetyMonitoringPolicy.htm.

9. Impact on the LABS parent study
    a. List of proposed clinical sites
    b. LABS resources required to conduct the ancillary study
    c. Relevance to LABS hypothesis and interpretation of results
    d. Impact on Data Coordinating Center for data management and analysis

C. Receipt Timeline

Ancillary study proposals must be submitted no less than 6 months prior to a funding source submission and/or starting date if funding has already been secured.

D. Application Review Process

Applications are to be submitted to the LABS DCC. Upon receipt, the DCC will review the application to insure that all the sections required above are included. Incomplete applications will be returned to the applicant for revision and resubmission, if appropriate. The 6-month receipt deadline is for a complete application.

Proposals deemed complete by the DCC will be forwarded to the Steering Committee.

Scientific and other criteria review (as detailed above) will be carried out by the Steering Committee.. Reviewers may be selected from within the LABS consortia or from non-LABS researchers with relevant expertise. Conflict of Interest will be evaluated on each reviewer. Reviewer expertise may include, but is not limited to, the scientific area(s) of the proposed ancillary study, analytical/statistical procedures, clinical study design and relevant methodological procedures.

The proposed study will be evaluated using the NIH criteria of Significance, Approach, Innovation, Investigator, and Environment. Each reviewer will be asked to provide a critique of the study and score from 1-5 (1.0-1.5, Outstanding; 1.5-2.0, Excellent; 2.0-2.5, Very Good; 2.5-3.5, Good; 3.5-5.0, Acceptable)

The SC will use the reviewers' critiques and scores to recommend approval or disapproval to the Steering Committee.

Appendix B: Policy for Non Renewable Sample Requests from LABS

The LABS consortium has a collection of urine, blood serum and plasma stored at the NIDDK Repository. Ancillary proposals that request the use of non renewable samples from LABS will abide by the ASC Guidelines with the following additional requirements and clarifications. The research plan should include the following specific information:

Background

1. Importance of the project, including the significance of both the study question and the specific project.

2. Justification for why LABS and LABS specimens are required and why other sources of similar samples are not appropriate. This section should explain how the proposed ancillary study's use of the samples relates to the design and outcomes of the parent study (LABS) that produced the requested samples. The question being posed by the investigator must be appropriate to the source of the biospecimens, how they were collected, prepared, analyzed, and stored, their age, and the phenotypic and other accompanying data. The serum, plasma and whole blood were collected and processed as per the following methods:

Serum	Three 7.5 mL Red Gray (Tiger-top) SST vacutainers	**Processing:** • Mix by inverting gently 5 times. • Let stand upright at room temperature for a minimum of 30 minutes but no more than 45 minutes. • Centrifuge at 1200 RCF (g) for 15 minutes at 4°C. • Store at -70°C
Plasma	• Two 10 mL Purple-top (EDTA) vacutainers • One 3 mL Purple-top (EDTA) vacutainer	**Processing:** • Mix by inverting gently 8-10 times. • Centrifuge at 1200 RCF (g) for 15 minutes at 4°C (may put on ice for up to 45 mins prior) • Store at -70°C
DNA (whole blood)	Three 8 mL Purple-top EDTA vacutainers	• Mix by inverting gently 8-10 times. • Keep tubes at room temperature. • **DO NOT CENTRIFUGE.**
Urine	1 mL	• Spot urine, not 24-hour fasting • LABS implemented urine storage in 2007, urine is not available on all baseline samples

Research Design and Methods

A. Sample Information:

1. Include detailed information about what samples are requested. LABS has a collection of urine, blood serum and plasma and DNA. If you will be combining the results from the LABS samples with those obtained from samples from other studies, explain how the requested samples will fit in with your overall study design.

2. Specify the time points from which the samples are requested (pre-surgery, 1 year after surgery, 2 years after surgery, etc.).

3. Specify sample selection criteria. For example, are samples requested from all LABS subjects or are samples requested from LABS participants with or without specified characteristics, clinical events or laboratory findings.

3. Include a clear justification for the amount of sample being requested. In all cases, applicants should only request the minimum volume needed for the study.

B. Project Details:

1. Hypothesis: There should be at least one important hypothesis that can be tested using the proposed methods and non-renewable samples provided from LABS participants.

2. Methodology: Describe how the requested samples will be used, including a description of the specific procedures by which the samples will be tested and analyzed and the quality control and robustness of the assay.

3. Power and effect size: Describe the power of the project and the anticipated size of a detectable effect.

4. Data analysis: Provide a detailed plan for data analysis. Include a brief summary of the team's expertise and experience and evidence that they can handle the analysis proposed.

5. Data management: Describe how the accompanying phenotypic data as well as the data from sample analysis will be managed. For example, who will have the main responsibility for organizing, storing, and archiving the data? Who will maintain computer data files and make needed work files available to those who will analyze the data? How will the privacy of information of beneficiaries in the files be guarded and guaranteed? Highlight experience with data management for large data sets, such as those to be produced by the proposed project

6. Sample management: Explicitly address how the samples will be held, managed, and processed. For example, who will have the main responsibility for storing and testing the samples?

C. Project Support: Describe whether there is current NIH funding to support the research project and if so, provide the grant number(s). If there is no NIH funding, briefly describe the source of funding to support the proposed project or the plan to apply for funding. If the application will not be reviewed by an NIH study section, please refer to guidelines for review of such proposals contained in Appendix A to the LABS Ancillary Guidelines. If the applicant

proposes to apply for funding subsequent to approval, approval of access to samples will be conditional on successfully obtaining funding. Conditional approvals will be valid for a period of up to 12 months.

D. Data Sharing Plan: Applicants must plan to return data derived from analysis of samples to the LABS DCC , in accordance with the LABS ancillary studies policy, along with appropriate quality measures. The plan should acknowledge the requirement to follow NIDDK instructions to either return or destroy the phenotypic data and unused samples to the NIDDK Central Repositories one year after the award of this project.

E. Human Subjects: Applicants must include in this section a statement of how the proposed research fits within the limitations of the subjects' informed consent.

Scientific Review Criteria

The LABS ancillary studies committee will consider each of the five review criteria below in the determination of scientific and technical merit.

Significance: Does the project address an important problem or a critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field? Is the proposed use of the samples highly significant?

Investigator(s): Are the PD/PIs, collaborators, and other researchers well suited to the project? Is the investigator familiar with the study that produced the samples being requested?

Innovation: Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach: Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Are potential problems, alternative strategies, and benchmarks for success presented? Are the requested samples uniquely suited for the requested study? Does the proposed research take advantage of the data associated with the samples? Does the quantity of sample requested match the intended use? Are sufficient preliminary data presented to demonstrate accuracy and robustness of the proposed assay?

Environment: Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the LABS subject population?

Impact on Inventory: How will this request impact the stored specimen inventory? For how many people will it deplete the inventory? How many samples will remain?

Review Timeline

The ASC will review proposals with specimen requests bi-annually beginning January 1st and July 1st of each year. Proposals are due by that deadline to undergo review by the committee. Investigators planning NIH or other grant submission deadlines must submit to the closest review date 6 months prior to the NIH deadline to allow for review by LABS and LABS committees.

Review Criteria Summary

- Clearly stipulate why LABS data and LABS specimens are required to complete the proposed work.
- Indicate the minimum number of subjects' samples needed to complete the proposal.
- Approval by LABS will be based on how well proposals meet the scientific review criteria, sample justification criteria, and the overall impact this sample request will have on the LABS biospecimen inventory..
- The above guidelines will be reviewed at least annually and may be edited or changed by LABS at that review time.