

# LONGITUDINAL ASSESSMENT OF BARIATRIC SURGERY (LABS)

## Ancillary Studies Guidelines

The Ancillary Studies Committee (ASC) 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 and 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 has designated the ASC to conduct an initial review of all proposed ancillary studies. Ultimately, the Steering Committee must approve all ancillary studies recommended for its consideration by the ASC to ensure that they 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:

Laurie Koozer  
University of Pittsburgh  
Epidemiology Data Center  
127 Parran Hall  
130 DeSoto Street  
Pittsburgh, PA 15261

Telephone: (412) 624-4003  
FAX: (412) 624-3775  
E-mail: [labs@edc.pitt.edu](mailto:labs@edc.pitt.edu)

The current submission process, described below, was revised in October 2005 based on experience with two prior cycles of applications. Potential applicants should, therefore, follow the current guidelines in preparing and submitting future applications.

**Letter of Intent:** To facilitate prompt review of the proposal, a letter of intent should be sent to the Data Coordinating Center at least three weeks before submitting the 3-page preliminary proposal. The letter of intent should include the title of the study, a brief description of the project (not to exceed 250 words), names of the investigators, a list of participating sites, and proposed funding sources. These letters will be circulated to the PIs of the LABS sites. Either at this point or during the subsequent review of submitted proposals (see below) LABS investigators may contact the PI of the proposed ancillary study to seek collaborative participation in the proposed study.

**Timing of Submissions:** *Proposals that will be submitted to the NIH for funding should be submitted to the ASC 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 proposals by its ASC and Steering Committees 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 that review the associated applications for funding.

RFA DK-03-022, which established the initial Ancillary Studies Program related to LABS, has now 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>). 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.

Proposals for ancillary studies to LABS for which funding has already been secured or for which application will be made to some other potential funding source 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. .

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

<b>Ancillary Applicant Action Item</b>	<b>Weeks/Months Prior to NIH Submission Deadline</b>
Letters of Intent to DCC	4 months
3-page preliminary proposals to DCC	3 months
Proposal PIs must contact DCC if they require DCC data management and analytical support 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 ASC 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:  
 Attn: Laurie Koozer, LABS Project Coordinator  
 University of Pittsburgh  
 Epidemiology Data Center  
 127 Parran Hall  
 130 DeSoto St.  
 Pittsburgh, PA 15261*

## **The Proposal**

Proposals for all ancillary studies must be submitted to the DCC for review by the ASC. *An accompanying 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 of biological samples required, and other data elements to be collected, including data required from the LABS core database;

[8] Projected costs.

## Ancillary Study Review Process

**ASC Review Criteria:** In referring proposals to the Steering Committee with a recommendation for final approval, ASC will give priority to studies which ASC believes: (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. Close collaboration with the participating LABS sites is necessary throughout this process.

**Initial Evaluation:** ASC will review submitted proposals at least monthly. LABS will not carry out an in-depth scientific review of those proposals that will be undergoing significant scientific scrutiny via a peer review process (e.g. NIH study section). The ASC will focus on the feasibility, overlap with LABS projects, and study/participant burden. A LABS Clinical Center coordinator assigned by the ASC will review the feasibility of the proposed study in relationship to LABS goals and resources. Proposals will initially be categorized 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. Based on further evaluation (see below), such studies may be referred to the Steering Committee with a recommendation for approval.

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. Based on further evaluation, such studies may be referred to the Steering Committee with a recommendation for approval.

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 referred to the Steering Committee with a recommendation for approval unless the overlap with main or sub-study protocols is minimal.

4) The ancillary study's aims are outside the interests of LABS. Such studies will not be referred to the Steering Committee with a recommendation for approval.

5) The ancillary study's aims could be met by an independent project, and do not require an affiliation with LABS. Such studies will not be referred to the Steering Committee with a recommendation for approval.

6) Irrespective of the relevance of the study's aims, an ancillary study that will make unacceptable demands on LABS patients, staff, or on the pools of available biological samples, will not be referred to the Steering Committee with a recommendation for approval.

**Scientific Review:** Proposals in categories 1 and 2, and possibly some in category 3, will be further evaluated by the ASC prior to their recommendation to the Steering Committee. The ASC review of ancillary study proposals that will be submitted to the NIH and undergo peer review will include a preliminary review of scientific merit, but will focus on the feasibility of the study for LABS as well as an assessment of any overlap or interference of work already being completed in LABS. . This review is for ASC purposes and 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 regular 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 ASC, supplemented with other experts as necessary, will conduct its own in-depth scientific review of a proposal.

During ASC review, all ancillary studies proposals will be circulated to the PIs of the six LABS Clinical Center sites for comment. Interested LABS investigators may contact the PI of the proposed ancillary study and request to participate as collaborators in the study. In addition, as appropriate, the ASC may recommend that the ancillary PI consider adding additional sites to provide added power, a more diverse population, or to contribute specific scientific expertise. The LABS Data 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 make a recommendation to the Steering Committee as to whether an ancillary study should be given initial approval. This recommendation will not only consider whether the ancillary study interferes with the LABS protocols, but will also consider whether it competes with other proposed ancillary studies for limited additional participant or staff time and/or biological resources (e.g. blood and tissues). To maximize efficient use of patients and other resources, the ASC 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. .

**Conditional Approval:** If the ASC determines that any given proposal contains elements that if adjusted would allow for approval, it will be given conditional approval and the PI will be notified with an itemized list of those elements that need to be altered and in what manner in order to gain ASC approval.

**Protocol Changes:** Applicant PIs must call to the attention of ASC no later than four weeks before the deadline for submission of the completed, final proposals any substantial changes from the approved three page application that appear in the final application document. This requirement applies whether the changes are investigator initiated or are made due to recommendations from a review group such as the ASC prior to submission to the NIH. Substantial changes include, but are not limited to, change of sites, PIs, endpoints, hypotheses and biospecimens needed, major changes in sample sizes, and merging of applications. Simultaneous with notification of the ASC of proposed changes, these modifications must also be conveyed to the DCC electronically, in a format that includes highlighting of modified sections, so that the DCC has adequate time to allocate LABS resources necessary to accommodate these changes.

In all instances of substantially altered applications, the ASC will re-evaluate and recommend to the Steering Committee whether the modified project still merits SC support as a LABS-approved Ancillary Study. Following their receipt, LABS will also compare all final application documents 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.

**Studies Proposing to Use Stored LABS Specimens:** ASC approval and *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. *Final* approval to begin such studies is also contingent on documented availability of necessary funding.

**Failure to obtain funding:** If, within 8 months of initial approval by the Steering Committee, an investigator is unsuccessful in obtaining the necessary resources, including funding, to conduct an ancillary study that would deplete the LABS blood or tissue repository, 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 Coordinating Center 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 ancillary study proposal to use LABS tissues/resources, accompanied by the scientific critique of the initial funding application, must be submitted via the Coordinating Center within the next 60 days for reconsideration by ASC. If the ASC recommends approval of the revised application to the Steering Committee, the Steering Committee *may*, at its discretion, keep the required specimens or other resources available for the project in question for a further 8 months, allowing time for submission of the revised application. However, the Steering Committee reserves the right to reallocate these LABS resources should they be required for another project that the Steering Committee approves. In the absence of such a revised application, the initial Steering Committee approval for the project will be withdrawn.

**ASC Conflict of Interest Guidelines:** During the evaluation process, if any ASC 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 ancillary study 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 applications received after March 1, 2005 is considered as approval for only one application for funding, with a date to be stipulated in the application and resulting LABS approval statement. Investigators who wish to resubmit a revised application after NIH review 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**

In addition to a favorable review by ASC, the Steering Committee will consider several additional issues before granting *final* approval to conduct an ancillary study.

**IRB Approval:** The Steering Committee requires that all ancillary studies receive necessary approvals from IRBs at the individual institutions involved. Documentation of IRB approval must

be submitted to the LABS Coordinating Center 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, particularly after LABS ends.

**Availability of Funding:** For ancillary study applications that require a further application to NIH or other organizations for funding, *initial approval* by the Steering Committee constitutes approval to apply for such funding. *Final approval* by the Steering Committee requires submission by the PI of the ancillary study application of documents establishing that a definite commitment for funding has been received. However, because several applications that compete for LABS resources may receive potential 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 such 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 Coordinating Center for additional data collection and statistical support, burden or other costs to Clinical Centers for sample collection and shipping, and burden or other costs to LABS participating patients). 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 cost to LABS.

**Agreement to Provide Severe Adverse Events Reports:** Ancillary study applicants must agree to submit to LABS such Severe Adverse Events (SAE) Reports as may be required by the Labs Steering Committee and/or Data Safety Monitoring Board. These reports are in addition to any SAE reports required by the IRB's 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 once again reaffirm their interest and ability to participate in the study at that time. If a LABS site cannot participate in an intended study after funding, 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 Coordinating Center to an ancillary study investigator is subject to the rules regarding release and use of data defined in the LABS Publications and Presentations Policy.

In general, *all* data collected by the ancillary study must be provided to the LABS Coordinating Center electronically and in timely fashion for integrating into the main database and analysis by the Coordinating Center. In return, ancillary study investigators will receive an analysis file containing both their data and approved, relevant data from the main study. 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 Coordinating Center may be negotiated between the PI of the ancillary study and the Coordinating Center prior to granting by the Steering Committee of final permission to proceed with the study.

If core LABS data are to be used as part of an ancillary study, any additional data or samples collected for the ancillary study will become part of the LABS archive, and management and statistical analysis of the LABS component of the data will, in general, be performed by the LABS Coordinating Center. However, as indicated above, in the case of specialized methods or those requiring unique forms of analysis, the Coordinating Center will consider requests that would delegate such analyses to the ancillary studies' investigators.

**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 through the Ancillary Subcommittee. 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 Ancillary Subcommittee will review the proposal to determine whether or not it should be recommended to the Steering Committee for final approval.

## **Non-NIH sponsored Ancillary Studies**

Proposals for ancillary studies that will seek to be funded from sources other than NIH (e.g. industry, foundations, other governmental agencies) will be evaluated in accordance with the procedures described above. In addition, it is the responsibility of the PI to obtain agreement from the sponsor through an appropriate contractual mechanism that all data relevant to the LABS ancillary study will be shared with the Coordinating Center and the Steering Committee. Conduct of sponsored ancillary studies also 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. If the ancillary study will involve industry support, the investigator should contact the NIDDK project scientist before beginning substantive discussions with any potential industry sponsor. Involvement of a study with industry may require a Cooperative Research and Development Agreement (CRADA) with NIDDK.

## **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 grant as well as the specific support for the ancillary study.

**Acknowledgement**

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.