



Teen-LABS Ancillary Studies Guidelines

1.0. Purpose

The Ancillary Studies Committee (ASC) will evaluate protocols that enhance the ability of Teen-LABS to: [1] document the efficacy and complications of bariatric surgery in the adolescent surgical patient and its role in the overall management of obesity prior to and through the emerging years of adulthood; and [2] address other important clinical, epidemiologic, and basic science questions related to teenage obesity and surgical intervention.

2.0. Definition of Ancillary Studies

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

The Teen-LABS consortium will collect a large and uniquely well-characterized sample of obese adolescents and will follow them before, during, and after bariatric surgery. To make the best possible use of this extraordinary resource, members of the Teen-LABS Consortium encourage other investigators to develop ancillary studies in conjunction with other investigators within and outside of Teen-LABS. Each ancillary study must include at least one Teen-LABS Co-investigator and must have the approval of the Principal Investigator at each Teen-LABS site proposed to participate in the ancillary study protocol. In addition, Teen-LABS investigators may request to join a proposed Ancillary Study.

The Teen-LABS Steering Committee (SC) 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 Teen-LABS staff or participating subjects or conflict with the aims of Teen-LABS. Data collection for funded ancillary studies may not proceed without the approval of the Steering Committee. Please refer to

the Ancillary Study Checklist for specific steps for progress of an approved ancillary study to Teen-LABS.

3.0. Submission of an Ancillary Studies Proposal

Potential applicants should follow the steps and guidelines described below in preparing and submitting applications.

3.1. Timing of Submissions: Proposals that will be submitted to NIH (or any other sponsor) for funding should be submitted to the ASC no less than 3 months prior to planned date of submission to the sponsor to assure that Teen-LABS review, input, and approval can be provided in ample time to meet sponsor deadlines. Teen-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 that are submitted to NIH for funding will be conducted by the NIH Study Sections that review the associated applications. For proposals that will not undergo future rigorous, scientific peer-review, the deadline for receipt of the completed full proposal will be modified to include 8 weeks for the ASC to conduct its own scientific review (see Scientific Review section). Deadlines for the various steps in the evaluation process for ancillary studies that are intended for submission to NIH and other sources under any of the above sets of deadlines are indicated in Table 1.

Proposals for ancillary studies to Teen-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 Teen-LABS for its approval at least three months prior to the intended project starting date, allowing Teen-LABS to conduct its own evaluation and impact analysis.

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

<u>Ancillary Applicant Action Item</u>	<u>Time Prior to Submission Deadline</u>
Letters of Intent to DCC	4 months
3-page preliminary proposals to DCC (See below)	3 months
Proposal PIs must contact DCC if they require DCC data management and analytical support	2 months
Proposals to DCC for minimal budget analysis or for those who want Teen-LABS data only	6 weeks
Completed proposals for NIH submission to DCC for distribution to Clinical	4 weeks
Centers for burden analysis and to ASC to confirm conformity with approved 3 page proposal	4 weeks
Completed proposals that require ASC scientific review	8 weeks

Upon NIH submission, send a complete hard as well as electronic copy of the submitted proposal to the DCC at the mailing address and email address below:

Rosemary Miller, RN, CCRC
3333 Burnet Ave. MLC 5041
Cincinnati, OH 45229-3039
Rosemary.Miller@cchmc.org

3.2. Materials Needed for Submission of Proposal

3.2.1. Step 1: Letter of Intent

A letter of intent should be sent to the Teen-LABS DCC. 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. The letter of intent should be submitted to the DCC at least three weeks before submitting the 3-page preliminary proposal (see below). Letters will subsequently be circulated to the PIs at each of the Teen-LABS sites.

3.2.2. Step 2. The Proposal

Cover Letter: The proposal should be accompanied with a cover letter of no more than one page that indicates *why the proposed study should be conducted as an ancillary study to Teen-LABS rather than as a separate and independent project.*

Proposal: Proposals should be concise, but contain sufficient detail to allow a thorough assessment of the relevance of the proposal to the goals of Teen-LABS, its scientific importance and possible impact on patient recruitment and follow-up, as well as any anticipated additional workload for Teen-LABS staff. Proposals will be 3 pages in length, single-spaced in an easily readable type font (not less than 11pt) 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] An abstract including (a) Background, (b) Specific Aims; (c) Clear statement of hypotheses to be tested; (c) Outline of the protocol, clearly indicating procedures to be performed on and samples to be collected from subjects, (d) List and brief description of any non-routine analytical methods employed; and (e) Informative reference citations.

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

[5] List of Teen-LABS sites contributing subjects or other resources, and any other collaborating Teen-LABS or non-Teen-LABS sites. Close collaboration with the participating Teen-LABS sites

through the entire process is highly encouraged. *For prospective studies that are being submitted to a funding agency, the proposal must be accompanied by letters from the PIs of all collaborating Teen-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 Teen-LABS sites must once again confirm their participation in the proposal and if participation is not possible at that time, another willing Teen-LABS site may be substituted with the consent of the Teen-LABS Steering Committee.

[6] Indication of numbers and sizes of biological samples required, and other data elements to be collected, including data required from the Teen-LABS core database

[7] Projected costs including budget for Teen-LABS DCC staff and analytical support if relevant.

4.0. Ancillary Study Review Process

4.1. 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 Teen-LABS' aim of examining a broad range of relevant research questions;
- (2) make important use of the unique Teen-LABS patient cohort;
- (3) do not interfere with or duplicate the main Teen-LABS objectives or those of other accepted ancillary studies;
- (4) produce minimal burden on Teen-LABS participants and minimal demand on Teen-LABS resources, such as blood samples and tissues that are also required for accomplishing the goals of the major Teen-LABS protocols;
- (5) have valid scientific merit; and
- (6) could not readily be accomplished as separate projects independent of Teen-LABS.

It is a goal of Teen-LABS to facilitate as many high-quality ancillary proposals as possible. Close collaboration with the participating Teen-LABS sites is necessary throughout this process.

4.2. Initial Evaluation: ASC will review submitted proposals at least monthly. Teen-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 Teen-LABS projects, and study/participant burden. The Teen-LABS Central Study Coordinator will also review the feasibility of the proposed study in relationship to Teen-LABS goals and resources. Some proposals may be highly appropriate for affiliation with Teen-LABS while others may entirely not fulfill qualifications to be an ancillary study. Thus, protocols will initially be categorized into one of five groups which appear below in decreasing order of appropriateness for the ancillary mechanism:

- 1) The ancillary study's aims are fully consistent with the overall goals of Teen-LABS, while distinct from those being addressed by the major Teen-LABS aims or protocols. The proposed study makes unique and valuable use of Teen-LABS assets including subjects, may involve collecting novel samples, and may also use data or samples collected for the main Teen-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 Teen-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 Teen-LABS protocols, and may utilize specimens collected for major Teen-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 Teen-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 generally outside the overarching goals of the Teen-LABS project. Such studies will not be referred to the Steering Committee with a recommendation for approval.

5) The ancillary study's aims are completely separate from Teen-LABS and could be met as a free-standing, independent project, and do not require an affiliation with Teen-LABS. Such studies will not generally be referred to the Steering Committee with a recommendation for approval.

6) Irrespective of the relevance of the study's aims, an ancillary study may not be feasible due to unacceptable demands on Teen-LABS subjects, staff, or on the pools of available biological samples. Such studies will be referred to the Steering Committee with a recommendation for disapproval.

4.3. 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 NIH and undergo peer review will include: 1) preliminary review of scientific merit, but will focus on the feasibility of the study for Teen-LABS, and 2) an assessment of any overlap or interference of work already being completed in Teen-LABS. This review is for ASC purposes only 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 protocols which have not obtained or will not obtain rigorous peer review (eg. proposals that will be funded by unrestricted grant support to a research group), the ASC, supplemented with other experts as necessary, will conduct its own in-depth scientific review of a proposal. The period of time required for an in-depth review will vary based on the complexity of the study but will generally not be less than 3 months or more than 6 months.

During ASC review, all ancillary studies proposals will be circulated to the PIs of the five Teen-LABS sites for comment. Interested Teen-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 Teen-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 Teen-LABS objectives.

During ASC review, all ancillary study proposals will be sent to the PI of the Teen-LABS DCC for review of the budget to assure that Teen-LABS DCC staff and analytical costs are appropriate.

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 Teen-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 subjects 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 limited Teen-LABS resources.

4.4. 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.

4.5. Protocol Changes: Applicant PIs must inform the ASC of any substantial changes from the approved 3-page application that appear in the final grant submission *no later than four weeks before the grant submission*. 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 sponsor. 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 to 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 Teen-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 Teen-LABS-approved Ancillary Study. Following their receipt, Teen-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 considerable but previously undisclosed modifications at that time. All protocol changes must be submitted to the ASC for approval prior to study implementation, as well.

4.6. Studies Proposing to Use Stored Teen-LABS Specimens: ASC approval and *initial* Steering Committee approval for an ancillary study to use stored Teen-LABS specimens will be contingent upon the availability of the requested specimen beyond the needs of core Teen-LABS protocols and approved ancillary studies already underway. Studies which seek to use biological specimens will be using stored resources which may not be replenishable. Thus, such studies will be rigorously reviewed for their scientific and societal value, uniqueness, and the likelihood of successful completion of the study. Final approval to begin such studies is also contingent on documented availability of necessary funding.

4.7. Failure to obtain funding: ASC approval of a study is valid for eight months and if, within 8 months of initial approval by the Steering Committee, an investigator is unsuccessful in obtaining the necessary resources, including funding, the initial Steering Committee approval of the project will be withdrawn and the Steering Committee may at that time approve other proposals, including those requesting to use the same specimens or variables as the unfunded study. 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 Teen-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 the 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 Teen-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. Studies that fail to obtain funding will need to be resubmitted to the ASC for reevaluation.

4.8. 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.

4.9. Duration of Initial SC Approval: The ancillary PI should specify the planned date of final submission of their grant application to the ASC in their proposal. Initial Teen-LABS approval should be considered valid for the project for only that one application funding cycle. This stipulation will also be specified in the Teen-LABS approval letter. Investigators who wish to resubmit a revised application after peer review must renew their Teen-LABS approval by submitting a new 3-page proposal to Teen-LABS in accordance with the schedule indicated in Table 1. The ancillary PI should attach the critique obtained after peer review as an appendix to the new 3-page proposal to aid the ASC in evaluation of the new proposal.

5.0. 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 Teen-LABS DCC before an ancillary study can be initiated in conjunction with Teen-LABS.

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

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 Teen-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 research projects to proceed in a manner that would not place an unacceptable burden on Teen-LABS subjects or other resources prior to awarding final SC approval. No data collection or use of Teen-LABS subjects, 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 Teen-LABS entailed by the proposal (e.g., staff time/burden, or other unanticipated costs to the Clinical Centers or 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 Teen-LABS participating subjects). 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 uncovered cost to Teen-LABS.

Agreement to Provide Severe Adverse Events Reports: Ancillary study applicants must agree to submit to Teen-LABS Severe Adverse Events (SAE) Reports as may be required by the Teen-LABS Steering Committee and/or Data and 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 Teen-LABS Sites' Participation: Prior to final Steering Committee approval of a funded proposal, each Teen-LABS site that is participating must once again reaffirm their interest and ability to participate in the study at that time. If a Teen-LABS site cannot participate in an intended study after funding, another willing Teen-LABS site may be substituted with the consent of the Teen-LABS Steering Committee.

Funded Ancillary Studies Must Document Their Willingness to Follow Teen-LABS Publication and Presentation (P&P) Guidelines: These guidelines are available on the Teen-LABS website for reference. Publications from Ancillary Studies are subject to these guidelines and require P&P approval prior to publication.

6.0. Data Issues

The release of any Teen-LABS data from the DCC to an ancillary study investigator is subject to the rules regarding release and use of data defined in an appendix to the Ancillary Study Guidelines. Teen-LABS will determine the timing of the release of requested data elements and that timing will be governed by the Teen-LABS data release policy (see Appendix).

In general, *all* data collected by the ancillary study must be provided to the Teen-LABS DCC electronically and in timely fashion for integrating into the main database and analysis by the DCC. 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 Teen-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 the analysis any special circumstances that would make these guidelines for data sharing impossible or undesirable. Reasonable and justified requests for limiting Steering Committee use of the data will be considered if they are in keeping with Teen-LABS data release policy guidelines.

If core Teen-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 Teen-LABS archive, and management and statistical analysis of the Teen-LABS component of the data will, in general, be performed or overseen by the Teen-LABS DCC.

However, as indicated above, in the case of specialized methods or those requiring unique forms of analysis, the Data Coordinating Center will consider requests that delegate such analyses to the ancillary studies' investigators.

Additional Data Requests for Funded Ancillaries: Funded ancillary studies seeking to receive data from the main Teen-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.

7.0. Costs

In general, the costs of all ancillary studies will be born by the ancillary PI. DCC costs will be recouped from the ancillary study. The DCC requires that funds be earmarked in any funding application after appropriate discussion with DCC staff.

8.0 Non-NIH sponsored Ancillary Studies

Proposals for ancillary studies that will seek to be funded from sources other than NIH (e.g. industry, foundations, and 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 Teen-LABS ancillary study will be shared with the DCC and the Steering Committee. Conduct of sponsored ancillary studies also must comply with all existing Teen-LABS, individual institutions within Teen-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 Teen-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.

9.0. Ancillary Study Progress

Ancillary study investigators are asked to provide progress reports to the DCC and subsequently the ASC quarterly, including data on recruitment, study progress, and plans. These reports will be reviewed by the DCC in conjunction with the ASC for regular study monitoring. Of specific importance are the notification of any proposed protocol changes prior to implementation and the plans for publications and presentations so that they can be routed through the Teen-LABS P&P Committee.

9.1. Protocol or Research Plan Modifications for Approved On-going Teen-LABS Ancillary

Studies: Teen-LABS Ancillary Principal Investigators must submit a description and justification of any protocol or research plan modifications to the ASC for review and approval prior to implementation. Examples include but are not limited to changes in: study population recruitment source, inclusion criteria or target number; procedures or instruments for data collection; or timing of data collection.

9.2. Monitoring of Teen-LABS Subjects' Research Burden:

A data collection form will be added to Teen-LABS subjects' visits to assess the number and type of research studies that each subject is participating in, to assess the nature of the subjects' research commitments and participation outside Teen-LABS at each participating site. This will include Ancillary studies

10.0. Publications and Presentations

Proposals for all abstracts, presentations, and publications utilizing data derived from Teen-LABS must be submitted for review and approval by the Teen-LABS Publications and Presentations Committee or SC prior to submission, in accordance with the Teen-LABS rules for publications and presentations.

Since ancillary projects must involve at least one Teen-LABS investigator in a collaborative relationship, each abstract, presentation, and manuscript should also include a Teen-LABS investigator as co-author to recognize their participation. This condition should be met unless extenuating circumstances exist 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 Teen-LABS Consortium grant as well as the specific support for the ancillary study.

Acknowledgement

In drafting these guidelines, the Teen-LABS ASC had the benefit of ancillary studies guidelines developed previously for the NIDDK-funded LABS consortium. LABS ancillary studies guidelines, 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.