Chapter 26

Ancillary Studies Policy

ANCILLARY STUDIES (AS)

Definition: An ancillary study is one based on information from LLFS participants in an investigation which does not coincide with a scientific aim or study question addressed by the LLFS, and requires new data, new assays or new material which are not present as part of the established LLFS.

Examples of types of AS include:

A. Studies requiring collection of data through additional questionnaires not originally used in the baseline or follow-up collections of LLFS.

B. Studies requiring additional exam procedures in LLFS participants. Depending on their duration and complexity, such procedures may require that participants pay a separate visit to the clinic site or to another testing location.

C. Studies using stored biospecimens or other previously collected materials.

D. Questions that expand LLFS scientific aims.

E. Questions that are not part of the LLFS scientific aims.

F. Pooling projects or consortia that wish to use LLFS samples.

Secondary analyses of already existing LLFS data is NOT an ancillary study and proposals regarding secondary analyses of LLFS data or material should be directed to the Publication & Presentation committee.

Local (one-center) vs. Multi-center Studies: AS proposals that would collect new data on participants may involve one or more or all LLFS Field Centers. However, proposers of AS are encouraged to take advantage of the unique characteristics of LLFS; therefore, an AS should be proposed as a single-center study only if involving all centers is not feasible or appropriate.

Who Can Apply for AS

A. Any LLFS Principal Investigator or co-Investigator may submit an AS proposal. The Center's Principal Investigator's signature is required.

B. Non-LLFS investigators may submit AS proposals. While non-LLFS investigators interested in analyzing existing LLFS data sets and stored biospecimens may wish to collaborate with a LLFS investigator (sponsor), a formal collaboration is NOT required. Non-LLFS investigators also do not need to be affiliated with a LLFS institution. However, a LLFS sponsor will be required for all ancillary studies that propose new data collection/contact with the LLFS cohort to ensure adherence to study protocols and procedures.

C. LLFS Investigators serving as Sponsors for non-LLFS AS PIs are responsible for the following:

1. Ensuring that the LLFS AS and Publications Policies are followed;
2. Serving as a liaison between the AS and the parent study;

3. Ensuring appropriate communication between the AS PI and the LLFS PIs during the AS proposal planning phase; and

4. Ensuring new data is shared with LLFS after the embargo period.

After approval by the LLFS Ancillary Studies committee and subsequently by the LLFS steering committee and OSMB in some cases (potential for increased participant burden or risks), the LLFS makes available a copy of its publications policy to the ancillary study investigators. When funding applications for an ancillary study utilizing LLFS biospecimens or creating new data are submitted, it is requested that a courtesy copy be sent at that time to the LLFS Scientific Officer at NIA (Dr. Nalini Raghavachari, nraghavachari@mail.nih.gov).

Proposals: LLFS encourages collaboration and invites investigators to propose and conduct ancillary studies. Such studies enhance the value of the LLFS and ensure the continued interest of the diverse group of investigators who are critical to the success of the study as a whole. To protect the integrity of LLFS, ancillary studies are reviewed and approved by the Steering Committee and in some cases the Observational Studies Monitoring Board (OSMB) before their inception. In general, ancillary studies require external (non-LLFS) funding, since no costs for an ancillary study can be borne by the parent study.

Funding: Funding for an ancillary study must cover the costs incurred by an LLFS study agency, such as the laboratories (e.g., to process and/or ship samples), and to the Coordinating Center (for tasks such as to process and ship analysis files, provide documentation, participate in statistical analysis, and integrate the new ancillary data back into the combined LLFS database). No funds for this purpose are available within the parent study. This applies to all ancillary studies that are initiated by both LLFS PIs/CO-Is and non-LLFS investigators.

What happens once funding is obtained/data is generated

A. When funded, AS investigators who are not LLFS investigators or who are not affiliated with the LLFS Institutions must sign an LLFS Data and Materials Distribution Agreement (DMDA) in order to receive study samples or data. Upon signing the DMDA, AS PIs must indicate that they are cognizant of the requirement to send the AS data to the LLFS Coordinating Center for inclusion into the LLFS database, and that the AS data are eventually made a part of the LLFS dataset available to outside investigators. This transfer is the responsibility of the ancillary study principal investigator.

B. AS investigators have exclusive rights to use the data generated by the AS for one year after the data set is finalized for analysis. However, access to LLFS data – except those needed for QC - will only be granted once the AS data has been received by the LLFS Coordinating Center. After the one year of exclusive use by the AS investigators is up, the Coordinating Center will incorporate the AS data into the main LLFS data base for use by other LLFS investigators and collaborators.

C. The AS must provide appropriate documentation to the Coordinating Center for the data to make them useful to outside investigators.

D. Left-over DNA and laboratory specimens must be destroyed; files of LLFS data are returned or deleted, as established at the outset of the collaboration.

Role of the LLFS Coordinating Center: After funding for the ancillary study has been awarded the LLFS Coordinating Center provides the ancillary study principal investigator with the data approved for use by the ancillary study. The distribution of biologic specimens to an ancillary study (if applicable) is coordinated by means of samples or lists prepared by the Coordinating Center specific to each ancillary study. Only the LLFS Coordinating Center is authorized to provide study data to an ancillary study. Costs derived from these tasks must be covered by the ancillary study.

Role of the Central Laboratories/Specimen Repositories: To the degree that an LLFS laboratory has the capability and the interest to conduct assays for an ancillary study, it is the parent study's preference that such assays be done at the LLFS laboratory. However, ancillary study investigators can use any laboratory for measuring any proposed biomarkers for ancillary studies. If laboratories other than the LLFS laboratory are used for biomarker measurement, the ancillary study principal investigator should ensure that the laboratory fulfill quality requirements and that adequate funds are allocated for both the LLFS laboratory and the Coordinating Center (if applicable) for identification of sample subsets (e.g. particular families are selected for an ancillary study), aliquot preparation and shipping of samples to another laboratory. The LLFS principal investigator responsible for a laboratory or specimen repository is responsible for the distribution of the biologic specimens approved for use by the ancillary study, based on samples/listings prepared by the Coordinating Center. Costs associated with these tasks must be covered by the ancillary study.

Approval of Applications for Ancillary Studies: The LLFS Ancillary Studies Committee is responsible for initial review of the ancillary study. Investigators provide a two to three page proposal following the format provided by the Ancillary Study Proposal Template. The Ancillary Studies Committee considers this information to assess the priority of the proposed study and determine its potential impact on the main study (LLFS). Highest priority is given to studies which: 1) do not interfere with main LLFS objectives; 2) have the highest scientific merit; 3) have objectives closest to those of LLFS; and 4) can draw on the unique characteristics of the LLFS cohort.

The Ancillary Studies Committee reviews the proposal to determine that it does not compromise, hinder, or jeopardize the conduct of the LLFS. Burden on LLFS participants must specifically be addressed and will be reviewed simultaneously by the LLFS Field Operations Committee. A review of proposed ancillary studies for scientific merit is not the primary responsibility of the LLFS ancillary study review process, but suggestions of a scientific nature may result from the review. Ancillary study proposals approved by the Ancillary Studies Committee (and Field Operations committee, if necessary) are sent to the LLFS Steering Committee and the NIA for final approval. The approval is valid for 3 years and then renewal can be applied for. The LLFS Steering committee will decide if the proposed ancillary study must be submitted to the OSMB, who recommends approval or disapproval to NIA. NIA approval is required before grant applications or requests for funding are submitted.

IRB Approval: Studies that will collect new data from participants must obtain a separate informed consent form from all ancillary study participants. This consent should clearly identify the ancillary study as one being performed in addition to the main study and inform subjects that their participation in the ancillary study is not necessary for them to continue in LLFS. All ancillary study proposals will need to obtain IRB approval through the single IRB at Washington University that manages the IRB for LLFS. Final IRB approval and the informed consent must be provided to the LLFS Steering Committee before implementation of the proposed study begins. If an approved proposal involves genetic studies, ethical, legal and social implications, as well as reporting of results, these must be proactively addressed in the proposal and approved by the single IRB at Washington University.

Time Line for Submission of Applications: Time Line for Submission of Applications: Because proposals for ancillary studies require review and approval by the parent study's Ancillary Studies Committee, the Field Operations Committee (if new data collection is proposed), and LLFS Steering Committees and also possibly by the OSMB at NIA, applications must be submitted to LLFS no later than 12 weeks prior to the intended date of submission to the funding agency (4 weeks if there is no participant burden). If funding is already available for an ancillary study, the ancillary study proposal can be submitted to the LLFS Ancillary Studies Committee at any time. To facilitate planning for these reviews and to prepare for a speedy response, it is recommended that the investigators notify the parent study in advance of their plan to submit an

ancillary study proposal. This letter of intent is not required but highly recommended, and should include an outline of the study aims, the proposed use of the parent study data, and the anticipated date of submission to the funding agency. Without this type of advance notification it can be difficult to convene a timely review by the ancillary studies committee, field operations committee (if necessary), and steering committee. Currently, the OSMB will be considering approval of ancillary proposals via e-mail on an "as needed basis" and a final decision will be provided by them within a two-week timeframe. In case we run into a situation where there are several ancillary proposals in line for OSMB consideration and with similar timelines, we will cluster the proposals for OSMB approval in order to make the most efficient use of the OSMB's time.

Example: Time Line for Submitting an Ancillary Study Proposal to LLFS:

- 6/01/06: Letter of intent addressed the Chair, Ancillary Studies Committee (optional, but recommended)
- 7/20/06: Deadline for submitting ancillary study proposal to the LLFS Ancillary Studies Committee, for review and feed-back.
- 8/03/06: Deadline for the Ancillary Studies and Steering Committee to submit the approved ancillary study proposal to the NIA (OSMB) for its review and approval.
- 10/01/06: First possible NIH submission date of the proposal, if approved as above

It is requested that a copy of the proposal be sent to the LLFS Project Office (Dr. Nalini Raghavachari, nraghavachari@mail.nih.gov) at the time it is submitted for funding.

Integrity and Disposition of the LLFS Data and Biologic Specimens: At the time of distributing LLFS specimens and/or information, the LLFS principal investigator responsible for that portion of the LLFS database (Coordinating Center, Central Laboratory) makes explicit arrangements with the ancillary study principal investigator for the security of these study materials, and for their disposition at the conclusion of the ancillary study. The safety and confidentiality of the LLFS data at the collaborating institution is the responsibility of the ancillary study PI, as is the appropriate disposition of these materials after the study has been completed. **Publications:** The Ancillary Studies Committee monitors the development of the ancillary studies, receipt of funding, initiation dates, and progress. Publications resulting from ancillary studies follow the same policies as described in the document on LLFS Publication and Presentation policy (please see publications policy).

Progress Reports: A written progress report on ancillary studies by the study's principal investigator is made yearly to the Ancillary Studies Committee. Progress Report Summaries will be made available, via a Tracking Log, on the Investigators' Only portion of the study website for review by the Steering Committee, OSMB and study investigators.

Proposal Cover Sheet: In order to expedite review of ancillary studies, LLFS has developed a proposal cover sheet that provides a synopsis of the impact of the study on LLFS. This should be followed by a brief 2-3 page proposal including aims, background and methods, including power calculations. The form can be found on the LLFS web page. The proposal cover sheet follows:

Cover Sheet LLFS Ancillary Study
Information and Projected Impact on LLFS

Title of study: _____

Initiating investigator(s) name, address, phone and fax numbers, e-mail address: _____

_____

Proposed LLFS Collaborators (if any): _____

Proposed starting and ending dates: _____

Source of funding; date of grant submission: _____

Summary of overall impact on the main study: _____

Summary of Field Center and Coordinating Center tasks involved:

Center	Examine participants (N)	Analyze samples (N participants)	Analyze data (Yes/No)

Description of participant, specimen and staff involvement:

A. Participants

1. Burden**:** Describe number of subjects needed; special characteristics of study population; age and sex distribution. Will participants be contacted, interviewed, or examined? If so, describe participant involvement and the specific time-point of planned data collection (Note that in most cases additional data should be collected after the main study data has been collected). Estimate time/effort required of each participant.

2. Safety monitoring: Will the ancillary study will have its own safety monitoring or will rely on the LLFS OSMB for this? Describe the safety implications of the study and plans for reporting adverse events to LLFS.

B. Stored materials (assuming repository - if plans include separate blood draw, state plans for managing specimens):

Sample Type (Serum, EDTA, DNA, etc.)	**Frozen** (Yes/No)	**Previously Thawed Okay** (Yes/No)	**Sample Volume**

C. Field Centers: Describe effort (and estimated time) required of staff at each participating center.

D. Study Coordinating Center: Describe effort (and estimated time) required of Coordinating Center staff. Specifically:

1. Will the Coordinating Center be involved in data collection, tracking, or preparation of forms or software? (Note that if these tasks will be completed by the Ancillary Study, a data file must be sent to the Coordinating Center.)

2. Will data analyses be done by analysts at the Coordinating Center?

E. Assurances: Assurances that data will be provided back to the main study for use by other investigators once the ancillary study objectives have been met.

Assurance that the Ancillary Study PI will report progress of the study from status of funding through data collection and manuscript publication.

Safety Monitoring (if appropriate), and confidentiality of individually identifiable LLFS participants must be assured.

PART 2: Description of the Proposed Ancillary Study

Please provide a brief (1-3 page) description of the proposed study. Include the following:

1. Background and rationale
2. Study aims: questions or hypotheses
3. Methods, including:
   - Participant involvement (if any)
   - Safety monitoring
   - Data to be collected
   - Data needed from the main study (including outcomes/events)
   - Sample size justification
4. Literature references

Notification Letter A

Date

PI Name and Address

Re: [Ancillary Study Proposal Title]

Dear Dr. XXXXX:

The LLFS Ancillary Studies Committee and the LLFS Steering Committee (and Observational Study Monitoring Board (OSMB)) reviewed the above-named ancillary study proposal and approved the proposal. You can now proceed with application for external funding and/or begin the study.

The Ancillary Studies Committee will review all ancillary studies at least annually for progress and productivity and prepare a report for the Steering Committee and the OSMB. Please review your responsibilities for reporting progress and for gaining prior approval for abstracts and manuscripts that are outlined in the LLFS ancillary study policy.

Best wishes for a successful ancillary study. We look forward to working with you on the LLFS study.

Regards,

Chair, LLFS Steering Committee

Notification Letter B

Date

PI Name and Address

Re: [Ancillary Study Proposal Title]

Dear Dr. XXXXX:

The LLFS Ancillary Studies Committee and Steering Committee reviewed the above-named ancillary study proposal and made a motion to grant provisional approval provided that you address the major comments below. Please forward your response in writing to me and the LLFS Ancillary Studies Committee chair, Kaare Christensen, by [2-week deadline from date of letter]. Your response will be reviewed and we will contact you when a decision has been reached.

Once approved by our Ancillary Studies Committee, we will forward the proposal to the Steering Committee and the Observational Study Monitoring Board. You will be notified in writing upon final approval, at which time you may proceed with application for external funding and/or begin the study.

Regards,

Chair, LLFS Steering Committee

Notification Letter C

Date

PI Name and Address

Re: [Ancillary Study Proposal Title]

Dear Dr. XXXXX:

The LLFS Ancillary Studies Committee and Steering Committee reviewed the above-named ancillary study proposal and has requested that the proposal be revised and resubmitted based on the comments listed below. Please resubmit the revised proposal by [2-week deadline from date of letter]. Upon review of the revised proposal, you will be contacted in writing regarding the Committee's decision.

Once approved by our Ancillary Studies Committee, we will forward the proposal to the Steering Committee and the Observational Study Monitoring Board. You will be notified in writing upon final approval, at which time you may proceed with application for external funding and/or begin the study.

Regards,

Chair, LLFS Steering Committee

Notification Letter D

Date

PI Name and Address

Re: [Ancillary Study Proposal Title]

Dear Dr. XXXXX:

Thank you for submitting the above-named ancillary study proposal. The LLFS Ancillary Studies Committee and Steering Committee reviewed the proposal and regrets to inform you that it has not been accepted based upon reasons listed below.

Regards,

Chair, LLFS Steering Committee