LIFE-MOMS ANCILLARY STUDIES POLICY
(05/17/2016 updated from 4/08/2016)

1.0 Definition of an Ancillary Study

An ancillary study is defined as a research protocol that uses the LIFE-Moms population to address additional but *relevant* scientific questions not being evaluated/ funded through the LIFE--Moms consortium.

1.1 Definition of Types of Studies

An ancillary study may be proposed as a Core, Super Shared, Shared, or Site-Specific study. Key measures and procedures that will be common to all of the trials are designated as 'Core' and will provide the basis for Consortium wide evaluations. 'Super-Shared' measures and procedures are defined as those collected in 4-6 of the LIFE-Moms trials. 'Shared' measures and procedures are defined as those collected in 2-3 of the LIFE-Moms trials. Site-Specific studies involve measures and procedures collected at one site only. An Ancillary study may use data and specimens already collected from participants enrolled in LIFE-Moms, or may propose to collect additional data or samples.

1.2 Ancillary Studies Committee

The Executive Committee appoints members to the Ancillary Studies Committee (ASC). There will be one member per site. The Committee will meet by teleconference to review applications.

Although all proposals are reviewed by each committee member, the RCU invites two members from different sites to serve as primary reviewers and to present the proposal to the committee with recommendations for acceptance or denial. Additional expertise may be brought in to review a proposal for scientific merit. All committee members will participate in the discussion, unless they are participating in the application being evaluated in which case they will recuse themselves from the review.

The committee reviews proposals for the following:

- scientific merit
    - evaluation of the ancillary study's contribution to LIFE-Moms aim of examining a broad range of relevant research questions
- burden or impact to the overall study
    - the ancillary study must not interfere with or hamper recruitment and retention and must not conflict with the LIFE-Moms study goals
- use of the LIFE-Moms cohort
- use of resources balanced against the probability of obtaining valuable scientific information (this is particularly important for nonrenewable resources such as specimens)
- competition or overlap for same samples with LIFE-Moms or other ancillary studies.

The final decision to accept or deny a proposal is made by majority vote. ASC may send the Ancillary PI comments and /or recommend revisions to an application. The RCU will prepare communications on behalf of the Ancillary Studies Committee.

1.3 Proposals that Require Ancillary Studies Review

If a site wishes to conduct additional analyses using their existing site-specific (non-Core/Super-Shared/Shared) outcomes data, the proposal does not need to go through the Ancillary Studies Committees (ASC) provided two conditions are met:

(1) the consent and/or study procedures does not need modification, and
(2) there is no additional study burden to either staff or participants.

The ASC should be notified of these proposals. The notification should include the same information as required in the letter of intent for other types of studies (see section 3.0). Collaborations of more than one site in an ancillary study will require the proposal to be reviewed by the ancillary study committee.

2.0 General Guidelines for <u>All Ancillary Studies</u>

Applications for ancillary studies should be submitted to the Ancillary Committee through the Research Coordinating Unit (RCU). Specific guidelines for submitting applications are described below. Studies must not place heavy demands on the existing infrastructure including LIFE-Moms personnel (time and cost to the RCU and clinical staff) or cause undue burden to the participants in terms of time, invasiveness, and/or safety.

Some studies may require an additional consent form, while others may embed consent to an ancillary study within the consent form for the primary study. All primary study consent forms should alert participants to the fact that they may be approached for further studies and they are free to decline to participate. Documentation of IRB approval for the ancillary study at individual institutions must be submitted to the RCU before data collection begins.

Funding must be obtained outside of the LIFE-Moms project. Sources of funding may include federal funding, grants from academic institutions, and other non-federal sources. The ancillary Principal Investigator should discuss the budget with the program officer at the *potential* funding institute.

Each ancillary study must include a LIFE-Moms clinical site and/or RCU Principal Investigator or Co-investigator. Principal investigators at the participating sites must submit a letter of support documenting that they will participate in the ancillary study and that they have read and approved the submitted application. <u>In the case of multi-PI studies, all of the PIs at the participating clinical sites must sign the letter of support</u>. Each letter must include the following statement “I have read and approved this ancillary proposal”. All co-investigators involved in the ancillary study should provide letters of support as well.

The Principal Investigator of a consortium-wide Ancillary study defined as any study making use of core or super-shared data and/or samples, must extend an invitation to all LIFE-Moms investigators to participate. Upon accepting an invitation, interested investigators should include in the response a description of what their contribution would be to the proposed study. Please note that as stated in the Publications and Presentation policy, all LIFE-Moms investigators will have an opportunity to participate in manuscript writing for any consortium-wide study.

LIFE-Moms data and samples (both core and shared) must only be used for the purpose of the approved ancillary study. Investigators seeking to use additional samples and/or data (beyond what was in the original approved ancillary study proposal) must request permission from the ASC.

If one or more similar or over-lapping proposals are received by the ASC, the ASC will urge the investigators to work together. If they cannot come to an agreement, the ASC will decide which proposal to approve.

Time sensitive studies must submit a letter of intent before they will be permitted to contact all PIs at the sites or submit a full ancillary study application. See section 3.0. *Letter of Intent for Time-Sensitive Studies.* Studies conducted at a single clinical site and/or studies proposing to use existing samples/data (i.e., non-time sensitive studies) are not required to submit a LOI. (Those types of studies should follow the instructions for submitting a full proposal. See section 4.0 *Guideline for Submitting Proposals* below.)

3.0 Letter of Intent for Time Sensitive Studies

A letter of intent (LOI) is to be submitted to the ASC by investigators who plan to propose a time-sensitive ancillary study that requires the collection of additional biological samples, data, and/or procedures beyond the LIFE-Moms Core/Shared or Super-Shared data collection at two or more sites. Investigators submitting a LOI must have a LIFE-Moms PI who agrees to serve as the ancillary study's sponsor.

The ASC will review the LOI for purposes of determining the scientific rationale, outcomes and compatibility with the LIFE-Moms aims and hypotheses, and the extent of overlap with other existing ancillary study proposals. The ASC will conduct a brief review to determine whether the proposal merits concept approval for further development. Investigators whose proposals are approved must also subsequently develop and submit a full ancillary study application for formal ASC review and ultimately SC vote. See section 4.0 *Guideline for Submitting Proposals* below.

The LOI should include the following components:

- a statement regarding the scientific rationale (2-3 sentences)
- a brief description of the research and methods (no longer than 2-3 paragraphs)
- a justification for collaboration with the LIFE-Moms study

- explanation of time-sensitivity
- a short biographical sketch from the proposing investigator
- a letter of support from the “sponsoring” LIFE-Moms PI
- a list of potential ancillary study co-investigators including LIFE-Moms collaborators (if known). If a site has already agreed to participate, this should also be noted
- a description of the targeted funding source (NIH/foundation/etc.) and anticipated receipt date

The letter is submitted to the ASC for review of the following:

- assurance that the proposed study is actually time-sensitive and has no potential to preempt the LIFE-Moms study aims/results
- consistency and lack of conflicts with LIFE-Moms goals and purposes
- appropriate justification for use of LIFE-Moms participants, data or samples
- potential for collaboration with other ancillary investigators
- overlap with other ancillary proposals

Procedure/timeline:

All LOIs should be submitted at least two weeks before the next regularly scheduled ASC call (4th Thursday of every month). The ASC committee will attempt to review the LOI by email. Approval by email vote must be unanimous with a minimum of 4 sites plus the RCU responding. If the vote is not unanimous (there are questions and/or disagreements) or fewer than 5 approvals are received, the LOI will be discussed during a conference call and approval will be by majority vote. A maximum of 4 weeks following submission should be allowed for a decision from the ASC.

If approved, 1) the ASC will notify the SC that the LOI has been reviewed and approved and 2) inform the ancillary study investigator that they may contact the relevant site PIs to determine willingness to participate in the proposed ancillary study. If the ancillary study investigator determines that a sufficient number of studies/sites agree to participate, the investigator is expected to submit a full proposal for review by the ASC.

4.0 Guidelines for Submitting Proposals

Studies using site-specific (only those requiring change(s) in study procedures/burden), shared, or core resources should submit a proposal to the ASC through the RCU. A proposal should be 3-5 pages and include the following information.

- a cover letter with a project title explaining the significance of the study and expected impact of the study on LIFE-Moms with justification for using the LIFE-Moms cohort and/or data and/or samples/specimens.
- a list of

    - LIFE-Moms sites participating in the ancillary study (for studies using or collecting shared or core resources)
    - other institutions that are participating
    - Principal and Co-investigators of the ancillary study by name and institution
- letters of support signed by all LIFE-Moms Principal Investigators at each participating site indicating that they have read and approved the study design and methods
- a description of the additional burden on LIFE-Moms staff and/or participants. [If the study will provide additional support for LIFE-Moms clinic staff, details should be discussed, including the relevant staff needed, the time commitment necessary, and the amount of salary support (as FTEs/calendar months) provided.]
- a section describing the research design:
    - background
    - specific aims
    - clear statement of the hypotheses to be tested
    - sample size justification for the primary hypothesis
    - outline of protocol clearly indicating procedures to be performed on and samples to be collected from participants
        - list of additional measurements to be obtained by the ancillary study including questionnaires, biologic samples, and physical measurements, including the quantity of each sample needed, if applicable.
        - amount of participant time needed to complete each additional measurement
        - list of core and/or shared data or samples requested from LIFE-Moms to complete the study, with justification, including the quantity of each sample needed, if applicable.
        - feasibility of proposed protocol
    - list and brief description of statistical and laboratory analytical methods
    - informative reference citations
- a description of the LIFE-Moms study resources needed and the budget that will be provided to cover these
    - For projects using core or super-shared resources, the budget must include appropriate resources for project coordination, data management and data analysis activities at the RCU. The PI from the ancillary proposal should discuss the project and budget with the RCU in advance.
    - For projects using site-specific or shared (but <u>not super-shared or core)</u> resources, the proposing group is responsible for data management and analyses, unless arranged otherwise with the RCU in advance.
        - Site-specific and shared data and specimens do not need to be submitted to the RCU.
    - The release of data and specimens between sites must adhere to the individual institutional requirements (i.e., data use agreement, material transfer agreements).

All ancillary study data is subject to the NIH data sharing policy. Ancillary data from super-shared or core protocols must be provided to the RCU for integration into the main LIFE-Moms database within two years of the end of the ancillary grant period for later submission to the NIDDK repository. Studies collecting additional bio-specimens at four or more sites must also plan to transfer remaining samples to the NIDDK repository.

4.1 Guidelines for Using Core and Super-Shared Biospecimens

The following applies to the NIDDK LIFE-Moms core or super-shared biospecimens. (Guidelines for data requests and non-core/non-super-shared biospecimen requests can be found in section 5.0.) Although proposals for use of stored biospecimens may be submitted at any time, the ASC will review Ancillary proposals that use core/super-shared samples three times a year (to correspond with NIH submission dates) as indicated in the table below. Investigators should allow up to 6 weeks for the review process.

Ancillary Proposal Receipt Dates	Ancillary Proposal Review Dates	NIH standard receipt dates
Oct 8	Nov 5	Feb 5
Feb 5	Mar 5	June 5
July 8	Aug 5	Oct 5

NIH RFAs using non-standard receipt dates and applications to non-NIH organizations will be reviewed on an as needed basis. In these instances, ancillary study investigators should contact the RCU as soon as possible to determine the schedule for ASC review.

The application should include a detailed description of the specimens needed. If multiple proposals are submitted for using the same sample type and one full aliquot is not needed for one study, the ASC will inform the investigators of the proposals that they will be required to share a single aliquot. This means that one lab will thaw, aliquot and ship to another lab. Payment for this process by the multiple proposals should be included in the grant application budget from the sites.

Applicants should indicate their willingness to collaborate with the LIFE-Moms study and other ancillary study investigators so that tests are not duplicated and relevant data can be shared among investigators for different purposes and objectives

4.2 Sample Types

Applications should clearly indicate which samples and how much volume are needed for their study. A list of sample types stored in the repository is listed below.

Maternal Samples (Core)

- Stored Collection Tubes (cryovials 0.5ml each)

    - Serum (cryovials 0.5ml each)
    - Heparin (cryovials 0.5ml each)
    - EDTA (cryovials 0.5ml each)
    - Sodium Fluroide (cryovials 0.5ml each)
    - Urine (cryovials 2.5 ml each)
    - DNA (PAXgene 8.5 ml whole blood)
    - RNA (PAXgene 2.5 ml whole blood)
- Placenta (Super Shared)
    - Chorionic Plate (sections in 3.0 ml cryovials)
    - Villous Tissue (sections in 3.0 ml cryovials)
    - Basal Plate (sections in 3.0 ml cryovials)
- Breast Milk (Super Shared)
    - Whole milk (cryovials 5.0 ml each)
    - Lipid layer (cryovials 5.0 ml each)
    - Whey layer (cryovials 5.0 ml each)

Infant Samples

- Cord Blood (Core)
    - EDTA (cryovials 0.5ml each)
    - Sodium Fluoride (cryovials 0.5ml each)
    - DNA (PAXgene 8.5 ml whole blood)
    - RNA (PAXgene 2.5 ml whole blood)
- Blood at 12 months (Super Shared) –

5.0 Timeline for Submitting Proposals to the ASC (for studies other than those using stored Core/Super-Shared Biospecimens) Ancillary investigators should submit their proposals far in advance of the funding agency application submission date. For planning purposes, guidelines are given below for determining the length of time for the ASC review and acceptance process. **[Guidelines for proposals requesting stored super-shared/core biospecimens can be found in section 4.1]**

5. 1 Timeline for Core and Super-Shared Ancillary Studies
Applications should be submitted 3 (or more) months prior to the submission date to the outside funding agency. This timeline permits 4 weeks for the ASC review and a 6 week allowance for revisions and additional reviews.

5.2 Timeline for Site Specific and Shared Ancillary Studies
Ancillary investigators should allow *at least* 2 weeks for initial committee review. This allows 2 weeks for ASC review. Upon review, the proposal may be sent back to the investigators for revisions. If revisions are required this may lengthen the review process.

6.0 Approval by LIFE-Moms Committees

The Ancillary Studies Committee has final authority to approve or reject a proposal. An official letter of approval or rejection to the ancillary study PI will be prepared by the RCU.

If the proposal is accepted, the final application to be submitted to the funding agency must be sent to the RCU a week prior to submission to confirm that the research plan is consistent with that which was accepted by the LIFE-Moms ASC.

7.0 Notification of Success/Failure to Obtain Funding

The ancillary study PI should inform the RCU of a positive funding decision within 5 days of receiving notice that their grant is going to be funded. Investigators whose application is not going to be funded should inform the RCU as soon as possible. If an ancillary study fails to obtain funding after two grant cycles following initial ASC approval, the project will be withdrawn to free up samples/tissues, other data, or participant time for other proposals.

7.1 Resubmission

If an ancillary study isn't funded and the investigators wish to revise and re-submit their grant application, the revised application must be submitted to the ASC for re-review. The resubmitted proposal should include a stand-alone description of the changes.

7.2 Timeline for review of re-submissions

The applicant should allow 6 weeks for reviewing a re-submission.

8.0 Ancillary Study Publication and Presentation Policy

Ancillary study manuscripts and/or presentations should be submitted for review by the LIFE-Moms Publications and Presentations Committee prior to submission, following the procedures of the LIFE-Moms Publications and Presentations Committee. Presentations and publications should include *at least one* LIFE-Moms Principal Investigator as a co-author (or include a justification as to why this will not occur) and acknowledge support of LIFE-Moms.

Core and super-shared data will not be released to Ancillary investigators until the main LIFE-Moms core and super-shared results are published. Ancillary studies that involve 3 or fewer participating sites may need to have their own site agreement between the site PIs and the ancillary study PI(s) about publishing results using non-core data.

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