

Ancillary Studies Policy Pediatric Acute Liver Failure (PALF) Study Group

GENERAL CONSIDERATIONS

The Pediatric Acute Liver Failure (PALF) Study Group is a NIH-funded network of twenty-one clinical sites and a Data Coordinating Center (DCC) whose goal is to study the etiology, diagnosis and treatment, and outcome of acute liver failure in children. PALF is centered around a large, longitudinal study which will collect data on new patients as well as biospecimens that include urine, bile, serum, liver tissue, cell lines derived from fibroblast culture and DNA which will be stored in repositories funded through the NIDDK. PALF investigations will include ancillary studies.

Definitions:

Exploratory Analysis: A proposal in which the investigator will

- a. Develop a preliminary hypothesis and limited data set to determine if sufficient data are available to support a Sub-study, Preliminary Study, or Ancillary Study
- b. Rely upon data collected as part of the primary study
- c. Be cost neutral and have no impact on PALF infrastructure, except for additional analyses
- d. Not result in published materials
- e. Require approval of the PALF Principal Investigator and DCC

Sub-study: A study in which the proposed investigation will

- a. Rely upon data collected as part of the primary study
- b. Be cost neutral and have no impact on PALF infrastructure (except for the additional analyses and manuscript/abstract preparation/review)
- c. Require approval of the PALF P and P Committee prior to analyses
- d. Require approval of the PALF Publication and Presentation Committee, Senior Steering Committee and representatives of the NIDDK prior to submitting abstracts or manuscripts

Preliminary Study: A study in which the proposed investigation will

- a. Require biosamples for analysis
- b. Rely upon data collected as part of the primary study
- c. Not require a separate protocol or informed consent
- d. Likely incur extra expense do to additional analyses and data collected from the biosamples
- e. May or may not result in an abstract or publication
- f. Require approval of the Senior Steering Committee prior to release of biosamples and conducting analyses.
- g. Require approval of the Publication and Presentation Committee, Senior Steering Committee and representatives of the NIDDK prior to submitting abstracts or manuscripts
- h. Ideally be the foundation for an Ancillary Study

Ancillary Study: A study in which the proposed investigation will:

- a. Supplement the primary study population with individuals who are *not* participants in the primary study and/or supplement primary study data with additional data collection from the study population (i.e. not part of the work scope of the primary study)
- b. Incur extra expense due to additional subjects or additional data required
- c. Require a separate protocol and informed consent
- d. Ideally developed in parallel with primary study
- e. Require approval of the PALF Senior Steering Committee and PALF Steering Committee before conducting analyses
- f. Require approval of the PALF Publication and Presentation Committee and representatives of the NIH-NIDDK prior to submitting abstracts or manuscripts.

Index Study: A study in which the proposed investigation will:

- a. Supplement the primary study population with individuals who are not participants in the primary study and/or supplement primary study data with additional data collection from the study population
- b. Possibly involve a surgical intervention or randomized trial
- c. Incur extra expense due to additional subjects or additional data required
- d. Require a separate protocol and informed consent
- e. Not share the objectives of the primary study
- f. Ideally developed in parallel with primary study
- g. Require approval of the PALF Senior Steering Committee and PALF Steering Committee before conducting analyses
- h. Require approval of the PALF Data Safety Monitoring Board and representatives of the NIDDK.
- i. Require approval of the PALF Publication and Presentation Committee, and representatives of the NIH-NIDDK prior to submitting abstracts or manuscripts.

Ancillary studies are studies are not part of the PALF longitudinal study, but propose questions and test hypotheses that are relevant to, and congruent with, the goals and purposes of the PALF Study Group. Such studies may require additional tests or data that are not routinely obtained in the main PALF longitudinal study. Ancillary studies may involve all PALF subjects and clinical sites, or subsets of either, depending on the eligibility criteria of the study, sample size needed, and interest of PALF investigators in participating. Ideally, an ancillary study will require modest demands on the time and effort of participants, clinicians, and clinical center study coordinators. These studies may also include the use of stored specimens (serum or plasma, DNA or cell lines, urine, bile and hepatobiliary tissues) and data already obtained from PALF subjects.

Ancillary studies must be independently funded by the investigator or by resources obtained by the investigator. Investigators proposing ancillary studies must seek funding from outside sources to conduct their research. Examples include funding obtained through investigator-initiated NIH research grant awards (R01's, R21's, R03.s, etc.), grants from academic institutions or foundations, or private funds. The PALF Steering Committee can provide a letter of support to funding agencies for proposals that have been approved by the PALF Steering Committee.

Investigators who are not a part of PALF must have a PALF investigator as a sponsor and collaborator. Investigators who are not part of PALF may contact any member of the PALF Steering Committee or its Chair who will help the investigator identify a potential appropriate collaborator.

When the study involves additional primary data collection by PALF, data management must be performed by the PALF DCC in coordination with the investigator, and the data from the ancillary study will become part of the PALF archive. Raw and "processed" data will be archived. Any additional data or sample collection will become part of the PALF study.

When the study involves only the analysis of samples from the PALF repository, data management may be performed by the investigator. However, the investigator must provide a dataset of the raw and processed data to be archived with the PALF database, which will be arranged with the DCC.

In both situations, all analyses of data must be confirmed by the PALF Data Coordinating Center and resources must be provided by the investigator to the PALF Data Coordinating Center for these efforts. Publications must follow the PALF guidelines.

SUBMISSION AND APPROVAL OF PROPOSAL FOR ANCILLARY STUDIES

Concept Proposal

Concept proposals should be a brief overview of a proposed topic of research, about 2-3 pages in length. The written concept proposal should include sections comparable to the following:

- Abstract: a brief summary of the proposed research that includes the primary research question, specific aims and hypotheses.
- Background and significance: a brief summary of supporting research and preliminary studies.
- Study design: a preliminary description of how the study will be executed including the study population, inclusion and exclusion criteria, primary outcome measures, randomized groups (if applicable), and research methods. An estimate of and justification for the sample size must be included.

- Impact on PALF: A description of the PALF data and specimens that are required and of any additional primary data collection. Specific size and amounts of samples requested must be included.
- Budget: a rough estimate of research costs (excluding clinical costs that can be charged to third parties) must be included. The budget should also include the incremental costs of the central resources of PALF, such as the DCC and the repository, that will be used and will need to be provided. It should indicate the source of funding and/or the plans to obtain external funding and the deadline for application for the funding, if appropriate.
- References. These are not included in the page limits.

All concept proposals should be submitted electronically to the PALF Research Administrator at least 3 weeks before a PALF Senior Steering Committee (SSC) meeting conference call or face-to-face meeting. The Research Administrator, DCC and Principal Investigator will ascertain that the concept proposal contains sufficient details (see above) to be presented. If the concept proposal is approved by the PALF Principal Investigator for presentation, it will be distributed to the PALF Steering Committee (SC) with a request that comments by members of the PALF SC be forwarded to the Research Administrator within 3 days of the scheduled SC conference call or meeting. The proposal will be added to the agenda of the SSC conference call or meeting and the investigator will present the proposal at the next Senior Steering Committee meeting or conference call. One primary reviewer will be chosen from the PALF SSC and two additional reviewers will be chosen among the members of the PALF Steering Committee (SC), who will summarize the strengths and weaknesses of the proposal on the conference call or at the meeting. After presentation and discussion, the investigator may withdraw the concept proposal from immediate voting if substantial revisions have been suggested by the Senior Steering Committee. (One possible type of revision is a recommendation that two or more proposals be merged or that a concept proposal be merged with a study already under development.) If so, the revised concept proposal would then be presented at a subsequent Senior Steering Committee meeting or conference call.

If the investigator decides to submit the concept proposal to a vote, the Senior Steering Committee will decide whether to advance the concept proposal to a protocol. Voting is by secret ballots that are counted immediately after they are cast. (If by teleconference, the PALF Research Administrator will conduct an e-mail poll.) A concept proposal is approved to advance to a protocol with a simple majority vote of the SC. If a concept is proposed and not approved by the SC, the investigator may develop the proposal independently with no obligation to the PALF.

Once approved, the investigator is responsible for expanding the concept and developing it into a protocol within 6 months (unless an extension is authorized by the PALF Senior Steering Committee) and submitting the full protocol to PALF for approval.

Protocol Committee

When the concept proposal is approved, a Protocol Committee is set up with the approval of the PALF Presentation and Publication Committee:

- The lead investigator will almost always be designated the Protocol Committee chair. In an unusual circumstance, co-chairs may be appointed.
- The lead investigator will work with the PALF Presentation and Publication Committee to identify and include investigators from other clinical sites and the DCC on the Protocol Committee depending on the involvement of those individuals in the conduct of the study.
- Lack of participation in protocol development does not preclude participation in the protocol when it is ready to be implemented with subject enrollment or sample collection; neither does it preclude authorship as long as all other criteria for authorship are met.
- The Protocol Committee, once established, is responsible for protocol development under the leadership of the Protocol Committee chair.

Once a Protocol Committee has been formed for a protocol, the names of all members and their institutional affiliation and email addresses are listed under the name of the committee chair.

The PALF Research Administrator will assign a number to the protocol; which should be placed at the top of the first page of the proposal and referred to as the study number in the subject line of all e-mail communications regarding the proposal.

Protocol

The protocol is an expanded version of the concept proposal, about 20-30 pages in length for index studies and 5-10 pages for ancillary studies, which should incorporate comments and recommendations made by the Senior Steering Committee at the initial presentation. The concept proposal should be expanded to a protocol as follows:

- Study Design: should now include specific details of study implementation.
- The sample size calculation should be provided with detailed justification. Investigators should work with the DCC for assistance with sample size calculation.
- Budget: a detailed estimate of research costs should be included.
- The protocol must also include a description of the proposed method of funding.

The protocol should also include:

- A list of clinical sites that have expressed intent to participate.
- PALF and other resources (including data, samples, etc.) required.
- Source of funding of project.
- Timeline.
- Relevance to PALF hypotheses and interpretation of results.

- Impact on PALF recruitment and conduct of study (details of the time and effort for subjects and work requirements for clinical center coordinators must be given).
- Risks and safety concerns.
- Impact on the Data Coordinating Center for data management and analysis.

If the protocol is to be funded by funds available to the investigator that do not require the study to undergo external peer review (i.e., discretionary funds, grant funds already available to the investigator, industry, etc.), the PALF Senior Steering Committee will develop either an internal or external peer review process for the proposal.

APPROVAL PROCESS

Protocols should be submitted to the PALF Research Administrator electronically for review and approval at least 3 weeks before the next Senior Steering Committee or teleconference meeting. The PALF Research Administrator and Principal Investigator will assure that the protocol contains sufficient details for presentation and it will then be added to the agenda and the investigator will present the protocol to the Senior Steering Committee. The protocol will be distributed to members of the PALF SSC. Members of the PALF SC are encouraged to review the protocol, make comments, identify concerns and forward these by email or letter to the PALF Research Coordinator. The protocol will be added as a part of the agenda before the Senior Steering Committee meeting for review and consideration. Two primary reviewers will be chosen from the PALF SC members and one reviewer from the PALF SSC before the meeting and they will present a summary of strengths and weaknesses of the protocol at the meeting, and ask questions of the protocol PI. Following presentation of the protocol, one of three decisions will be made:

1. The Senior Steering Committee will recommend that the protocol be revised and re-presented to the PALF at a subsequent Steering Committee teleconference or meeting; or
2. The Senior Steering Committee decides not to approve the protocol; or
3. The Senior Steering Committee decides to approve the protocol.

Voting is by secret ballots that are counted immediately after they are cast. Approval of a protocol requires a majority of the Steering Committee. Each member of the Steering Committee will also assign two priority scores for each study: one with respect to scientific merit using the NIH review criteria of significance, approach, innovation, investigator and environment, with a grade of 1 – 5, 1 being the highest merit and 5 being the lowest merit; and the second with respect to the impact on PALF resources using the same scoring system.

Approved PALF ancillary study protocols are submitted to the DSMB for evaluation and critique if necessary. The investigator may be invited to attend the DSMB meeting or that portion that relates to the protocol. The NIDDK

Program Director will apprise the investigator of the DSMB's comments and suggestions.

The initial approval for an ancillary study that would significantly impact the PALF serum, DNA or tissue repository is for a period of 270 days (nine months). If the investigator submitted a grant proposal for external funding which was not successful and informs the PALF Research Administrator that he/she intends to resubmit an amended proposal in the next cycle or following cycle, the approval will be extended for up to an additional 365 days (one year). Otherwise the authorization to use the specimens will be withdrawn and the Steering Committee will consider other proposals to use the specimens. Within 5 working days of receiving a decision from the funding source (e.g. NIH), the investigator is required to inform the PALF Research Administrator of the decision; and if unsuccessful, whether a revised application is planned. Within 3 working days of being notified that the specimens are no longer committed to the investigator, the PALF PI will inform Steering Committee members of the availability of the stored specimens for other ancillary studies. All proposals (re-submission and new proposals) must be sent to the PALF Research Administrator for review.

Individual sites wishing to join in an ancillary study may do so at any point during its submission, by notifying the PALF Research Administrator and the principal investigator of the ancillary study.

TIMING AND PROCEDURES FOR SUBMISSION

Concept proposals and protocols should be sent to the PALF Research Administrator at least **three weeks before the scheduled meeting or teleconference of the PALF Steering Committee** (via the address below).

A full protocol must be submitted no less than 8 weeks prior to a funding source submission date or starting date if funding is available. This allows at least 4 weeks for Steering Committee review of the revised protocol and a mail ballot.

One paper copy plus an electronic copy on disk or via e-mail of the proposal should be sent to:

ACKNOWLEDGEMENT:

In drafting these guidelines, we had the benefit of referring to guidelines from the NIDDK-sponsored Biliary Atresia Research Consortium (BARC) study and Cholestatic Liver Disease Consortium (CLiC).