Pediatric Acute Liver Failure (PALF) study group

Ancillary Studies Policy

1. Background

The Pediatric Acute Liver Failure (PALF) study group is a NIDDK-funded network of nineteen clinical sites and a Data Coordinating Center (DCC) whose goal is to study the etiology, pathogenesis, diagnosis, prognosis, and treatment of acute liver failure in children. The core studies of the PALF are: (1) a prospective observational database of infants, children and adolescents with acute liver failure, and (2) a double blind, randomized, placebo-controlled trial of intravenous N-acetylcysteine (NAC) in children with acute liver failure. To make the best use of this data registry and stored samples, the PALF study encourages investigators, both inside and outside of the study group, to develop ancillary studies.

2. Definition of ancillary study

Ancillary studies propose questions and test hypotheses that are relevant to, and congruent with, the goals and purposes of the PALF study yet they are distinct from the core studies of the PALF study. Such studies will often require information in the observational database but may also involve additional study sites, investigators, tests, specimens, data, procedures, or patients that are not included in the core studies. These studies may include the use of stored specimens (e.g., serum, DNA, hepatobiliary tissue) from PALF study subjects. Ancillary studies may involve any or all PALF study subjects and clinical sites, depending on the eligibility criteria of the study, sample size needed, and interest of center investigators. An ancillary study should not interfere with or duplicate activities of a main study, a substudy, pilot or feasibility study, or previously approved ancillary study.

3. Ancillary Studies Committee charge

The Ancillary Studies Committee does the following:

- Develops the policy for review and approval of ancillary studies.
- Reviews applications for ancillary studies and makes recommendations for approval or disapproval to the Steering Committee.
- Maintains a list of all proposed ancillary studies indicating approval status and the liaison. For approved studies, the list will indicate initiation date and the centers participating in the ancillary study.

- Maintains a list of allocations or commitments of existing or future samples to central and to ancillary studies.
- The list of all proposed ancillary studies and the list of allocations and commitments of existing or future samples will be available on the PALF website (www.palfstudy.org).

4. Overview of the Submission and Review Process

Investigators wishing to conduct an ancillary study must complete an application. The PALF Ancillary Studies Committee will review the application for innovation, investigator capability, science, alignment with PALF goals, potential overlap with existing studies, and feasibility. The Ancillary Studies Committee will make a recommendation to the PALF Steering Committee as to whether the ancillary study should be approved; the PALF Steering Committee must approve the ancillary study for it to proceed. Investigators who are responding to a program announcement or applying for funding must gain PALF approval for the study before submitting their application to a funding organization. An ancillary study proposed by investigators who are not members of the PALF study group must have a PALF investigator as a sponsor and collaborator.

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 and take into account the demands on the time and effort of participants, clinicians, the DCC and clinical center study coordinators. Examples include funding obtained through investigator-initiated NIH research grant awards (R01's), grants from academic institutions, or private funds.

5. Process for Submitting an Ancillary Study

An ancillary study is proposed to the PALF by submitting a completed PALF Ancillary Study Proposal (SP) form to the Data Coordinating Center. This form is available on the investigator portion of the PALF website (www.palfstudy.org). An external investigator proposing an ancillary study can obtain the form through a Steering Committee member who sponsors or collaborates in the ancillary study.

Information required:

- The principal investigator for the ancillary study and his/her institutional affiliation.
- Key investigators for the ancillary study and their institutional affiliations

- Name of the PALF Steering Committee member who will serve as sponsor and member(s) who are anticipated to be collaborator(s)
- The study title
- Anticipated start date and length of the study.
- Concept proposals (3 pages maximum length) including the following sections:
    - 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 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 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 data collection.
    - List of PALF sites contributing patients, and any other collaborating PALF or non-PALF sites.
    - A plan of analyses and the proposed role of the DCC in the analyses. When the study involves additional data, data management must be performed by the PALF Data Coordinating Center and the data from the ancillary study will become part of the PALF archive. Any additional data or sample collection will be stored in a separate database. When the study only involves analysis of samples from the PALF repository, data management may be performed by the investigator. However, the investigator must provide the dataset to become part of the PALF archive. Regardless of data management, all analyses of data must be performed or confirmed by the PALF Data Coordinating Center and resources provided to the PALF Data Coordinating Center for both data management (if applicable) and statistical analysis efforts. Publications and presentations resulting from ancillary studies to PALF must follow the PALF guidelines.
    - 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 the PALF study group, such as the DCC and the repository that will be used. Contact with these resources to obtain cost

estimates is required. It should indicate the source of funding or the plans to obtain external funding and the deadline for application for the funding, if appropriate.

- References.

6. Process for review of submitted proposal

- All concept proposals should be submitted electronically to the PALF DCC for review by the Ancillary Study Committee.
- Any Ancillary Studies Committee member(s) proposing an ancillary study, or affiliated with the institution of an investigator who proposes an ancillary study will be excused from reviewing.
- The Data Coordinating Center will circulate the submitted ancillary study application to the primary reviewer, who is assigned by the committee chair, and then to members of the Ancillary Studies Committee with instructions that they are to send their comments (see below for what they are to comment on) to the chair of the Ancillary Studies Committee by a specified date. The chair will collate the comments and prepare a written memo to the Steering Committee specifying the Ancillary Studies Committee's recommendation for approval or disapproval. The Steering Committee will review that recommendation at their next meeting or conference call and make a decision for approval or disapproval. If the meeting or call is not within 30 days, the review and voting will be conducted via email. The principal investigator of the ancillary study and the PALF CRN liaison will each receive a copy of the memo directing the Ancillary Studies Committee to review the study application (so that they know the time frame for review) and a copy of the memo from the Steering Committee specifying the decision for approval or disapproval.
- The proposal will be assessed by the Ancillary Study Committee members on the basis of science, alignment with PALF goals, and feasibility. A conference call will be scheduled to identify points of clarity. The committee chair will ensure sufficient expertise is present on the Ancillary Study Committee to provide a meaningful vote. If the expertise on the committee is not sufficient, the chair will work with the principle investigator and NIDDK representative to identify additional resources. Voting is by secret ballots cast within 10 working days of receipt of the concept proposal. Votes may be "approve", "conditionally approve" or "disapprove". Conditionally approved proposals may require additional information from the investigator proposing the study.

- Votes not received by the deadline will be counted as abstentions. A minimum of 5 votes are required for a quorum. Votes will be counted by the Project Coordinator at the DCC who will then notify the Ancillary Study Committee chair of the result immediately after they are cast. The Ancillary Study Committee chair will report results to the Steering Committee who will then vote by secret ballot within 10 working days of receipt of the Ancillary Study Committee chair report.
- A concept proposal is approved to advance to a protocol with a simple majority vote of votes received. If a concept is proposed and not approved by the SC, the investigator will be informed by the Ancillary Study Committee chair of the reason(s) for disapproval or deferral. The investigator may elect to revise the concept proposal. Once approved, the investigator is responsible for expanding the concept and developing it into a protocol within 6 months.

7. Full Proposal submission and review

- The full proposal is an expanded version of the concept proposal, which should incorporate responses to comments and recommendations made by the Ancillary Study and Steering Committees. The full proposal follows the format of an NIH grant submission. Details on study design, sample size calculation, budget and justification, analyses, resources required from the DCC, samples required, timeline, proposed funding source, relevance to PALF, and burden to PALF must be included
- All proposals must be submitted electronically at least 3 weeks before an Ancillary Study Committee meeting or conference call. Two members of the Ancillary Study Committee will be assigned as primary reviewers and will summarize the proposal. For ancillary study proposals that will be submitted to the NIH and undergo peer review, the ASC will make a preliminary determination of scientific merit. 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 detailed review of the scientific merit of a proposal. When feasible, three independent reviewers will critique the proposal and submit their findings to the ASC for a final decision with respect to scientific merit. In all instances, within the limitations of staffing, the ASC will endeavor to transmit to

the PIs of applications receiving unfavorable scientific reviews the key criticisms that led to the unfavorable decision.

- The proposal must be accompanied by letters from the PIs of all collaborating PALF sites and any other collaborating scientists indicating their roles in the project and their willingness to participate.
- In addition, one PALF coordinator will assess the impact on PALFSG resources as acceptable or unacceptable. Voting is by secret ballots counted at the DCC.
- Following presentation of the protocol, one of three decisions will be made:
    - 1. The Ancillary Study Committee recommends to the investigator that the protocol be revised. This will be reported to the Steering Committee.
    - 2. The Ancillary Study Committee recommends disapproval to the Steering Committee.
    - 3. The Ancillary Study Committee recommends approval to the Steering Committee.
- The PALF Steering Committee will be given the recommendation of the Ancillary Study Committee. If it concurs with the recommendations of the Ancillary Study Committee, then the PI will receive notification of the decision within one week of the Steering Committee call or meeting. If the proposal is approved, then the PALF Steering Committee chair will provide a letter of support for the approved proposal.

8. Implementation of an ancillary study

- Once a protocol is approved by the Ancillary Study Committee, it is placed on the prioritization list. Each time a new protocol is added to the list, the Steering Committee will reorder the priorities of all the protocols taking into account the priority scores assigned during the voting.
- The initial approval for an ancillary study that would utilize stored samples from the repository is for a period of 270 days (nine months). If the investigator submitted a proposal for external funding which was not successful and informs the Executive Committee that he/she intends to resubmit an amended proposal in the next cycle or following cycle, the approval will be extended for 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 about funding, the investigator is required to inform the DCC of the decision; and if unsuccessful, whether a revised application is

planned. Within 3 working days of being notified that funding was denied and no subsequent application is planned, the DCC will inform Steering Committee members of the availability of the stored specimens for other ancillary studies.

- Re-submissions must undergo the same review as original submissions.
- Individual sites wishing to join in an ancillary study may do so at any point during its submission, by notifying the Data Coordinating Center and the principal investigator of the ancillary study.

9. Additional Data Requests for Funded Ancillaries

- Funded ancillary studies seeking to receive data from the PALF study group 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.

10. Ancillary Studies Committee membership, election, and voting

- The Ancillary Studies Committee has eight voting members: 4 clinical center principal investigators, one clinical coordinator, a representative from the Data Coordinating Center, and an NIDDK representative. The committee chairperson (initially appointed by the Study Chair [Dr. Squires] and, thereafter, elected from among clinical center PIs by the Steering Committee), will vote in the case of a tie.
- The Data Coordinating Center will coordinate the election process. Steering Committee members will be queried for their interest in being on the committee. A ballot with their names will be circulated for a mailed vote by Steering committee members. Selection of the winner will be by highest number of votes. There will be separate elections for chairperson and for committee members. In the case of tie votes, the Executive Committee will decide the issue.
- The chairperson and members from the clinical centers serve for 2-year terms. Terms for the initially appointed chair and members will run for 2 years from the date of the initial

study review conducted by the committee. Data Coordinating Center and NIDDK members are appointed by the DCC PI and the NIDDK Project Officer, respectively..

- Members and chairs may serve unlimited terms.

11. Ancillary Studies Committee operation

- The Ancillary Studies Committee is a subcommittee of the PALF Steering Committee. The PALF Data Coordinating Center supports the operations of the Ancillary Studies Committee by arranging Committee conference calls, receiving submitted applications for ancillary studies, administering the process for review of submitted applications, writing correspondence for the Committee, maintaining the lists of ancillary studies and allocated/committed samples, the document and correspondence files relating the Committee's activities, and overseeing all voting procedures (i.e., elections, proposal approval).