Procedures for Evaluation and Approval of Ancillary Studies (AS)

GENERAL GUIDELINES

Among the types of ancillary studies envisaged in DILIN are the following:

1. Studies that involve the collection of data from or about DILIN study subjects, using procedures or measurements that were not included in the original DILIN protocol(s). An example is collecting detailed pedigree information from all DILI cases.

2. Studies that involve analyses beyond those envisaged by the DILIN investigators on data already being collected according to the DILIN protocol(s). An example is investigating a new genetic hypothesis for association with the occurrence of drug-induced liver injury.

All qualified scientific investigators are encouraged to conduct ancillary studies as long as such studies are judged to be scientifically sound and not likely to compromise or have an adverse effect on the main DILIN studies or their subjects.

All proposed ancillary studies (and their amendments, if any) must be submitted to the Ancillary Studies Committee for initial review and approval. Proposals for new ancillary studies may be initiated by any qualified investigator but must include at least one DILIN investigator from a participating center as either PI or co-PI. The DILIN investigator will have the overall responsibility for the AS, including the process of study approval and its execution. Amendments typically will involve changing or adding specific aims, recording of data, laboratory tests to existing ancillary studies, but will not change the goals of those AS's.

If the AS involves proposed support from or activities of commercial organizations, the NIDDK project office must be contacted and must approve, prior to any detailed discussions with company representatives (**Attachment 1**).

THE PROCESS OF SUBMISSION OF AS PROPOSAL:

Submission of a proposal for a DILIN AS is a two-step process:

1. Submission of a brief Summary of Concept; and, if the Summary is approved

2. Submission of a full AS Proposal.

Summary of Concept:

A one page concept description should be forwarded to DCRI, the data coordinating center for DILIN, for circulation among the AS committee. The concept page should contain the title of the project; principal and co-investigator(s); hypothesis; a brief description of background, aims, numbers of patients or samples required, reasons for doing this study in DILIN; outside collaborators; and expected cost (Attachment 2). Within 10 working days of receipt of this summary description, members of the AS committee (exclusive of the lead center(s) on the proposal) will vote whether to authorize development of a full AS proposal. As part of any affirmative vote, the AS committee members will indicate whether outside expert review will be needed for the full proposal. At the discretion of the chair of the AS committee, voting will be by email or conference call, For approval, the concept will require a simple majority of votes of members of the AS Committee casting votes.

Full AS Proposal:

After approval of the concept by the AS committee, the proposers are authorized to prepare and submit a full proposal. Amendments to previously approved studies may either be incorporated into or appended to the original proposal. The full proposal should follow the NIH grant application format (form SF424). Follow the instructions, except as indicated below:

- Do not include a Face Page
- Put title of AS and Name of PI and co-PI (usually from a different center) on the first 2 lines of the Description (section BB)
- Budget: Budget sections will be used to describe the budgets. It is not required that the budget be cleared with each institution's business office, but the estimate should be close to what would have been submitted. After approval of the proposal, a formal budget must be submitted through the business offices of participating centers following the format required by the NIDDK contracts' office. Budgets must include any additional expenses that will be incurred by the DILIN clinical centers and the Data Coordinating Center to make DILIN resources available to the ancillary study.
- Biographical Sketches for key personnel.
- Do not include Other Support
- Complete Resources section as appropriate
- Research Plan.

Include:

A. Proposal, Five page limit, single spaced:
   Aims/Hypothesis
   Background, rationale, significance, relation to aims of the DILIN
   Design and methods
   Anticipated results
   Analysis (including sample size justification)
   Anticipated impact of the AS on the DILIN studies and resources.
   Problems and pitfalls

B. Literature Cited

C. Draft of consents (regarding additional visits, blood needed, genetic tests, etc.)

D. Note the amount of liver tissue, blood, DNA, and patient time required at each visit. Use the table in **attachment 3**.

3. Evaluation and Approval of AS Proposal

The full proposal will be reviewed by the AS committee by teleconference or in conjunction with a SC meeting (attachment 4). Outside expert opinion may be solicited, at the discretion of the AS committee or its chair. The AS committee will approve the proposal as is, reject outright, or reject in current form with request for modifications by a simple majority vote.

Proposals that have been rejected with request for modifications at first submission may be resubmitted up to 2 more times. If they are still not approved, they must be withdrawn from further consideration.

Once approved by the AS committee, the proposal must be approved by a majority of the SC members before the AS may be implemented. If funding will be required, a source of funding must be identified prior to SC approval.

4. Progress Reports and Periodic Reviews

Annual progress reports for all approved AS's shall be provided to the DILIN Steering Committee. These reports shall be similar in form and content to the Annual Reports to NIH for active RO1 awards. Steering Committee decisions to continue Ancillary Studies shall be contingent on satisfactory scientific progress being made and little or no adverse effects on the main DILIN studies or their study subjects.

5. Publications

All abstracts, presentations, reports, and publications forthcoming from the Ancillary Studies shall come under the aegis of the DILIN Publication Policy. Proposals for such abstracts, presentations, manuscripts, etc., must be submitted to, reviewed, and approved by the DILIN Publications Subcommittee, according to the Publications Policy of the Network.

ATTACHMENT 1 - AS PROPOSAL-- DISCUSSIONS WITH INDUSTRY

1. Contact the NIDDK project office before beginning substantive discussions with any potential commercial sponsor or collaborator.

2. Explain to the company the process for approval of AS's in DILIN.

3. In addition to the three approvals (concept, full proposal, and SC approval) needed for any AS, a collaboration between the NIDDK and industry will need to be evaluated to determine what type of agreement is appropriate.

4. In general, industry funding for AS's will come from the sponsor to NIDDK and will be added to the contracts of the participating centers.

5. Business negotiations with potential sponsors should be through NIDDK. Individual Investigators should not make any promises or commitments to companies regarding their involvement in DILIN.

6. The PI and co-PI will work closely with NIDDK on negotiations with potential sponsors.

ATTACHMENT 2 – AS CONCEPT PROPOSAL

1. Title

2. Principal and Co-Investigator(s)

3. Hypothesis

4. Abstract:

- Background
- Aims
- Number of Patients and/or Samples Required
- Reasons for Doing This Study in DILIN

5. Outside Collaborators

6. Expected Costs and Sources of Funding

7. ATTACHMENT 3 - PATIENT AND TISSUE REQUIREMENTS

Complete and submit with full AS proposal

Visit	DNA (amt in mcg)	Blood # patients, ml	Patient Time # patients, min	Other (describe) # pts, amount

ATTACHMENT 4 -- REVIEW CRITERIA FOR FULL PROPOSALS

1. Relevance to the goals of DILIN. The **goal** of the trial is to identify and characterize subjects with DILI and to identify genetic, nutritional, and environmental factors, which may influence development, severity, or course of DILI. How well does the proposal support this goal? Does the study overlap with stated goals and objectives of existing DILIN protocols or ancillary studies?

2. Importance of the question: Does the study represent sound science? Is it likely that this question will still be of interest at the end of the study?

3. Qualifications and interest of the investigator(s). Are the investigators capable of carrying out the AS and remaining involved and responsible for its duration?

4. Study Design. Is the hypothesis well formed? Can valid conclusions be drawn? Is the analysis plan reasonable?

5. Burden to the study. Are the patient and coordinator time and the amount of liver and blood acceptable? Is there adequate funding for any additional expenses that will be incurred by the DILIN clinical centers and the Data Coordinating Center to make DILIN resources available to the ancillary study?

6. Uniqueness: Can the goals of the proposed ancillary study be met in settings other than the DILIN?

7. Scoring: Each reviewer will provide a single summary score using the NIH scoring system for investigator-initiated grant applications:

1.0 – 1.5	Outstanding
1.5 - 2.0	Excellent
2.0 – 2.5	Very Good
2.5 – 3.0	Good
3.5 – 5.0	Acceptable
Unacceptable	