Liver Cirrhosis Network Ancillary Studies Policy

The Liver Cirrhosis Network (LCN) is a multi-institute NIH-funded (NIDDK, NCI, NIAAA) network consisting of 10 clinical sites and a scientific and data coordination center (SDCC). The purpose of the network is to characterize the natural history of compensated cirrhosis through a longitudinal cohort study and determine the impact of statin use on clinical outcomes in patients with compensated cirrhosis in a randomized controlled trial (RCT).

Investigators wishing to conduct or participate in Ancillary Studies in conjunction with the Liver Cirrhosis Network should read the conditions for review and conduct of Ancillary Studies described below and complete the attached items. Contact the Liver Cirrhosis Network Ancillary Studies Committee with questions.

Key contacts include:

1. **Chair**: Rohit Loomba; University of California San Diego (UCSD); roloomba@health.ucsd.edu
2. **Vice Chair**: Arun Sanyal; Virginia Commonwealth University (VCU); arun.sanyal@vcuhealth.org
3. **Scientific and Data Coordination Center (SDCC)**: Northwestern University Data Analysis and Coordinating Center (NUDACC): lcn@northwestern.edu

1.0 GENERAL POLICY

To enhance the value of the Liver Cirrhosis Network studies, the Steering Committee welcomes proposals from investigators to carry out Ancillary Studies. To protect the integrity of Liver Cirrhosis Network, all ancillary studies must be reviewed and approved by the Ancillary Studies Committee, Executive Committee, Steering Committee, and (in some cases) Data Safety and Monitoring Board (DSMB). Unless exempt from review according to the Common Rule, ancillary studies must be approved by an Institutional Review Board (IRB) prior to initiation of the study. The guiding principles of the Ancillary Studies processes are: innovation and discovery, rigor, and flexibility.

2.0 DEFINITION OF AN ANCILLARY STUDY

An Ancillary Study is defined as research or data collection involving Liver Cirrhosis Network participants or specimens, using any technique, procedure, questionnaire, or observation other than those set forth in the Liver Cirrhosis Network cohort and clinical trial protocols. Ancillary studies may also involve non-LCN study sites, investigators, specimens or data collection, procedures, or treatments. The LCN Ancillary Studies process is not intended to be a mechanism to support pilot studies.

There are several categories of ancillary study:

1. **Integrated**: These studies are conducted prospectively and are integrated within one or more of the main LCN studies. Analyses will be carried out by the SDCC.
2. **Adjunctive:** These are prospective studies that require procedures or testing beyond those included in the main LCN studies. Analyses may or may not be carried out by the SDCC.
3. **Use of samples**: These studies may be prospective or retrospective and involve use of biospecimens collected in one or more of the main studies. Implicit with the request for samples will be the provision of limited data sets by the SDCC. Analyses may or may not be carried out by the SDCC.
4. **Use of data:** These studies may be prospective or retrospective and involve the use of data collected by one or more of the main studies. Analyses may or may not be carried out by the SDCC.

3.0 REQUIREMENTS FOR APPROVAL OF AN ANCILLARY STUDY

Refer to **Appendix A** for a map of the ancillary studies review process.

3.1 Considerations for Approval

All proposed Ancillary Studies must be reviewed and approved by the Liver Cirrhosis Network Executive Committee, Steering Committee, SDCC, and, for proposals that involve additional participant procedures or data collection, the DSMB before submission to a funding agency. After funding is obtained, the proposed Ancillary

Study must be reviewed and approved by the sIRB/IRB prior to implementation. As revisions are made to the proposal/protocol during this process, the Ancillary Studies Chair, in consultation with the SDCC and NIH, will determine whether the changes are significant enough to need re-review by the Steering Committee and/or DSMB.

The proposed study must:

- Meet requirements of the highest scientific merit.
- Not impose an undue burden on participants (e.g., in terms of time requirements or causing physical or mental discomfort) that will interfere with Liver Cirrhosis Network if it involves collection of additional data or biospecimens.
- Put minimal demand on scarce Liver Cirrhosis Network resources such as backup blood samples.
- Require the unique characteristics of the Liver Cirrhosis Network participants to accomplish its goals.
- Not interfere with or impede the completion of the primary or secondary objectives of Liver Cirrhosis Network.
- Not adversely affect participant cooperation or compliance with the Liver Cirrhosis Network protocols.
- Not create a serious diversion of study resources (personnel, equipment, or study samples) or investigator/staff time at the clinical centers or the SDCC.
- Be relevant to Liver Cirrhosis Network and align with the overarching goals of the LCN.
- Include details about its unique opportunity for acquisition of new scientific knowledge.
- Include adequate experimental design, methodology and data analysis plans.
- Show adequacy of the investigator and research environment.
- Address the burden of the study on the enrolled Liver Cirrhosis Network participants and the clinical centers.

The ancillary study investigators must:

- Agree to utilize the SDCC's database for data entry, management, and storage.
- Have adequate resources to effectively complete the project, including both financial support and personnel, as appropriate.
- Plan to acknowledge the LCN in any abstracts, publications, and other pieces of dissemination.

3.2 Personnel Requirements

Ancillary Study proposals may be submitted by investigators participating in Liver Cirrhosis Network, or by investigators who are not part of Liver Cirrhosis Network. **If the Liver Cirrhosis Network Ancillary Study Principal Investigator (PI) is part of the Liver Cirrhosis Network Steering Committee**, the Ancillary Study PI is the Ancillary Study Liaison between the Steering Committee and the Ancillary Study team**.**

If the Ancillary Study PI is <u>not</u> part of the Liver Cirrhosis Network Steering Committee, the Ancillary Study **must include a co-investigator** who is a voting member of the Liver Cirrhosis Network Steering Committee. In this case, the Ancillary Study co-I who is part of the Liver Cirrhosis Network Steering Committee will be the Ancillary Study Liaison.

The Ancillary Study Liaison will be the primary point of communication between the Liver Cirrhosis Network and the Ancillary Study applicants. The Ancillary Study Liaison is responsible for the following tasks:

1. Determining interest in Ancillary Study participation from all other LCN clinical sites, and for informing the respective LCN site PI(s) of the site's desired participation.
2. Submitting the Ancillary Study application to the SDCC at all points of contact.
3. Acting as a mentor to the Ancillary Study PI if the Ancillary Study PI is a junior investigator.
4. Providing a yearly written progress report.

Additionally, the Ancillary Study must include at least one site-specific co-investigator or site PI from each site represented in that study. For instance, if an Ancillary Study proposes to use specimens from LCN clinical centers

site 1, site 2, and site 3, then a Liver Cirrhosis Network co-I or site PI from sites 1, 2, and 3 must all be co-Is on the Ancillary Study.

Prior to submitting the Ancillary Study proposal, the Ancillary Study Liaison should consult each LCN clinical center PI independently about participating. LCN clinical center PIs who wish to participate in the ancillary study should be given the opportunity to review and critique the one-page proposal summary, before submission of the application to the SDCC. **No clinical center will be required to participate in an Ancillary Study.**

3.3 Funding Requirements

Ancillary Studies require external funding. Examples include studies funded by National Institutes of Health (NIH) research awards or grants from academic institutions or private sources (e.g., foundations, pharmaceutical companies, etc.). An Ancillary Study must have sufficient funding to cover the costs incurred by, if applicable:

1. The LCN clinical centers
2. The LCN Central Laboratory or Biorepository (e.g., to process shipments and ship samples, if the study wishes to utilize their services)
3. Contracts with outside laboratories for specimen management, analysis, and storage (e.g., to process and analyze samples, if the study wishes to utilize an outside lab)
4. The LCN SDCC (e.g., for tasks such as database development, preparing and documenting analysis files, participating in statistical analysis, and integrating the new ancillary data back into a combined database), and
5. The sIRB (if a study qualifies for using an sIRB under the Common Rule and/or funding agency policy, the study team is encouraged to utilize the Advarra sIRB. If the study does not qualify for using an sIRB under the Common Rule and/or funding agency policy, the study team may utilize a local IRB).

Funds are not available for these purposes within the LCN budget. The Ancillary Study proposal must identify the anticipated source of funds.

3.4 Specimens, Data, and Analyses

Ancillary Study data must be collected through the existing LCN database, which is housed at and maintained by the SDCC. If the study wishes to utilize the Liver Cirrhosis Network Central Laboratory or Biorepository for specimen management, the Ancillary Study budget must include appropriate effort and cost for the Central Laboratory or Biorepository to manage these tasks, if specimens are to be sent to an outside institution for analysis.

Management and analysis of the specimens can be contracted to outside institutions. The costs of that contract must be included in the budget.

Statistical support for ancillary study analyses may come from the LCN SDCC statistical team or from statistician(s) outside the SDCC. If the investigator would like to obtain support from the LCN statistician(s) for analysis, then the investigator should work with the LCN SDCC to determine the most appropriate approach to statistical support for the study.

If the investigator plans to enlist support from statistician(s) outside of the SDCC, the LCN SDCC statistician(s) will have the opportunity to review the analytic strategy during the ancillary study review process, and they will review the final analyses as part of the Publications and Presentation Committee prior to publication.

4.0 REVIEW OF ANCILLARY STUDIES PROPOSALS

4.1 Overview

An Ancillary Study Proposal must be reviewed and approved by the Ancillary Studies Committee, Executive Committee, Steering Committee, and an appropriate sIRB/IRB prior to implementation. The study may require review by a DSMB, but that decision is often deferred to the (s)IRB overseeing that study. If the Executive Committee and/or NIH deems it necessary, they may require DSMB review prior to initiation of the study, but

this decision would be made on a case-by-case basis. The Liver Cirrhosis Network Ancillary Studies Chair or a designated member will discuss concerns about a proposal with the applicant and opportunities for clarification/revision will be provided. An Ancillary Study must receive approval from the Liver Cirrhosis Network Steering Committee before grant funding is requested from an external funding agency. The Ancillary Study Liaison will work with a dedicated Project Manager from the SDCC to process submissions.

See Appendix A for a timeline of the review process. Overall, the applicant usually should allow 2.5 - 3 months for the review process, prior to submission to the funding agency.

4.2 Preliminary Proposal Review

The Ancillary Study Liaison will submit a one-page proposal summary (Appendix C) to the SDCC. The SDCC will review for completeness and will share it with the Ancillary Studies Committee Chair and LCN Executive Committee for initial review. The Executive Committee meets weekly, on average. If the one-page proposal summary is sent to the SDCC less than two full business days prior to the meeting, the proposal will be discussed at the following meeting.

The Ancillary Studies Committee Chair, in consultation with the SDCC and Executive Committee will perform a preliminary scientific review to ensure consistency of the proposed Ancillary Study with the LCN priorities. Specifically, the initial review will ensure:

1. The proposal does not interfere with any of the current activities of the LCN studies or other Ancillary Studies.
2. Ensure it does not create redundancies across LCN activities or other Ancillary Studies.
3. Identify any other general difficulties, inconsistencies, or incompatibilities.

Any concerns about a proposal at this stage will be discussed with the applicant and opportunities for clarification/revision provided, as appropriate. Additionally, the Executive Committee may decide that clarifications or revisions do not warrant further consideration by the full Steering Committee and thus may reject the proposal at this stage. If a proposal is rejected at this stage, the Executive Committee will inform the Steering Committee at the next meeting and provide written feedback to the Ancillary Study Liaison.

4.3 Review by the Steering Committee

Following preliminary scientific review and approval by the Executive Committee, the Ancillary Study PI will develop the one-page proposal summary into a full proposal, including budget (Appendix D). The investigator will submit the full proposal to the SDCC.

The SDCC will review the full proposal for completeness, and then send it to the Ancillary Studies Chair. The Ancillary Studies Chair will assign two reviewers to the proposal. The reviewers will score the proposal within two weeks of receipt. The reviewers will share their full reviews with both the Executive Committee and the Steering Committee both via email, in advance of the full Steering Committee meeting, and during the next monthly Steering Committee meeting. The SDCC will facilitate this process as needed. The Steering Committee should have at least two business days to review the proposal and the primary and secondary reviewer critiques prior to the Steering Committee meeting at which the proposal will be discussed.

The Steering Committee meets monthly. Thus, if a full proposal is sent to the SDCC less than two weeks prior to a Steering Committee meeting, it will likely be assigned to the following meeting. This will ensure the Ancillary Studies committee members have had the opportunity to review and critique the proposal in advance. If there is a time constraint on the proposal, the Executive Committee and/or Steering Committee may have the opportunity to convene an ad hoc meeting and/or resolve voting and recommendation via email.

A proposed Ancillary Study will require a majority vote (more than 50%) by the Steering Committee to be approved. Each of the 10 grantee clinical centers are allowed one vote; the NIH is collectively allowed one vote; and the SDCC is allowed one vote. Members of the Steering Committee who are also part of the Ancillary Study

team are allowed to be part of the discussion and vote; however, the Ancillary Study Liaison (and the site which they represent) will recuse themselves of voting.

The Steering Committee will make one of four determinations regarding the Ancillary Study proposal, based on the criteria listed in section 3.1, Considerations for Approval. The SDCC will facilitate final voting by email after the Steering Committee discussion, to allow LCN Steering Committee members to confer with other LCN investigators at their site prior to sending their final vote.

The Steering Committee will also designate the timeline for progress reporting required for each Ancillary Study (see section 6.2, Progress Reports).

Table 1. List of Steering Committee determinations

Decision	Meaning	Feedback	Resubmission Instructions
Not Approved	Fewer than majority votes for approval, with no possibility of revisions.	Written feedback from the Ancillary Studies Committee will be provided, explaining the decision.	N/A, resubmission is not allowed.
Tabled	The Steering Committee does not have enough information to vote.	Written feedback will be provided, explaining the additional information needed.	Respond to the feedback, send to SDCC. The proposal will go back to the full Steering Committee for review and vote.
Pending Approval	The Steering Committee agrees (with at least a majority vote) that the proposal will be approved if certain revisions are made.	Written feedback will be provided, explaining the revisions upon which the Steering Committee agreed.	Respond to the feedback, send to SDCC. If the Ancillary Study team agrees with the revisions requested, the revised proposal will go to the Ancillary Studies Chair to determine if the revision requests have been met. If the Ancillary Study Chair/Committee does not agree with the revisions requested, give a detailed and supported explanation. The proposal will go back to the full Steering Committee for review and vote.
Approval	The Steering Committee agrees (with at least a majority vote) that the proposal is approved as written.	Written documentation of the approval will be provided.	N/A. Future revisions to the proposal must be reviewed by the Ancillary Study Chair to determine if any significant changes have been made that need to be reviewed by the Steering Committee.

4.4 Submission to External Funding Agency

If the applicant requests a letter of support for inclusion in application for funding and the Steering Committee has voted to approve the ancillary study (contingent on funding), the SDCC will provide the applicant a letter on behalf of the Steering Committee to indicate the approval.

4.5 Biospecimen Hold

If the Ancillary Study Proposal includes utilizing specimens already collected or being collected, then these specimens will be put on “hold” upon submission of the proposal application to the funding agency for a period of six months. It is the responsibility of the investigator to inform the SDCC of the funding-agency review score, when available. Based on the score, the Steering Committee will decide whether to continue the hold in anticipation of funding and extend it for up to one additional year. If the applicant secures funding prior to submitting the Ancillary Studies proposal to the Steering Committee, then the hold will begin as soon as the Steering Committee approves the proposal. If funding is not acquired and/or sIRB approval is not obtained, the hold will be released and the biospecimens may be utilized or reserved for other Ancillary Studies.

4.6 Revision and Resubmission to Funding Agency

If the funding agency does not fund the proposal after the first submission, but the PI decides to revise and resubmit during another round, the Ancillary Study Liaison should send the revised proposal introductory information (Appendix C), research strategy, specific aims, budget, and applicable summary of changes/tracked versions to the SDCC. The SDCC will forward the revised proposal to the Ancillary Study Chair for review. The Ancillary Studies Chair, in consultation with the Executive Committee, will review the proposal to determine if any significant changes have been made that need to be reviewed by the Steering Committee.

Thus, the timeline for this step could be between two weeks and nearly two months, depending on whether additional reviews by the Steering Committee are needed. If significant changes are made, the Ancillary Study Liaison should consult with the SDCC early in the process, to assess the timeline.

4.7 Review by the sIRB/IRB

Upon approval for funding, unless exempt from review according to the Common Rule, the Ancillary Study must be approved by an sIRB/IRB prior to initiation of the study. Final approval for a proposed Ancillary Study rests with sIRB/IRB. Ancillary Studies not approved by the sIRB/IRB cannot be conducted, and it is the responsibility of the Ancillary Study PI to ensure sIRB/IRB approval and compliance with all Human Subjects' Research requirements according to US regulations.

If the sIRB/IRB requires changes to the protocol, the Ancillary Study Liaison must communicate these revisions to the Ancillary Studies Chair after sIRB/IRB approval. The Ancillary Studies Chair, in consultation with the Executive Committee, will review the protocol to determine if any significant changes have been made that need to be reviewed by the Steering Committee.

4.8 Review by the DSMB

On occasion, the sIRB/IRB and/or LCN Executive Committee and/or NIH may request that the Ancillary Study be reviewed by a Data and Safety Monitoring Board (DSMB). It is the responsibility of the Ancillary Study PI to ensure DSMB review and approval prior to protocol initiation in these cases. Involvement of the overall LCN DSMB for this process will require NIH approval and assistance. Review by the Liver Cirrhosis Network DSMB only focuses on how the Ancillary Study proposal fits in with the Liver Cirrhosis Network study; it does not constitute study-specific safety and monitoring. The Liver Cirrhosis Network DSMB may agree to act as the ancillary study's safety and monitoring board, but the Liver Cirrhosis Network DSMB will collectively make this decision; otherwise, it is the ancillary study PI's responsibility to find his or her own Ancillary Study DSMB as appropriate. All DSMB related matters must be approved by executive committee and/or NIH prior to initiating an ancillary study.

4.9 Changes to an Approved Ancillary Study

Once an ancillary study is approved, no changes can be made to the study without additional review. If the investigator wishes to make changes, these must be submitted for review to the SDCC, who will forward them to the Ancillary Studies Chair. The Ancillary Studies Chair, in consultation with the Executive Committee, will review the protocol to determine if any major or minor changes have been made that need to be reviewed by the Steering Committee. All changes will require submission to and approval by the sIRB/IRB.

A minor modification is a minimal change in the hypotheses, specimens needed or analyses to be performed in an approved Ancillary Study. Minor modifications meet the following criteria:

1. Overall scope of project remains unchanged, including overarching aims
2. No new specimens needed
3. No additional budget requested from the LCN (integrated studies only)
4. Minimal additional effort from the SDCC, as determined by the SDCC

A major modification is a change of scope, a request for more specimens, requires additional budget, or a request for more than minimal additional effort from the SDCC, as determined by the SDCC.

The investigator requesting the modification should write a short summary of the requested modification, including a brief justification.

Approval process for Minor Modifications

a. The investigator submits the minor modification request to the SDCC. Chair of the Ancillary Studies Committee will review the minor modification request to ensure it meets the definition of a Minor Modification (anticipated timeline within one-two weeks).
b. The SDCC and Ancillary Studies Chair circulate the proposal to the Ancillary Studies Committee and the Executive Committee.
c. Members of Ancillary Studies Committee and the Executive Committee vote on Approval/Disapproval. The vote should be conducted by e-mail but may be conducted during a conference call. The anticipated timeline for this process is within one month.
d. If the Minor Modification is approved, then:
    1) The SDCC notifies the Investigator in writing that the modification was approved. The investigator can then proceed with the proposed work once approved by the IRB/sIRB
    2) The approval of the minor modification is noted in the minutes of the next Ancillary Studies Committee conference call and the minor modification is attached to the minutes of the conference call.
    3) The LCN Steering Committee is notified of the minor modification at the next LCN Steering Committee Meeting or Conference Call.

Approval processes for Major Modifications

Requests for Major Modifications need to be evaluated and approved using the procedures described above for full proposal review and in Appendix A.

Failure to adhere to Ancillary Studies Policies and Procedures may lead to sanctions against the investigator.

4.10 Summary of Responsibilities of the Ancillary Studies Chair

The following are the responsibilities of the Ancillary Studies Chair. If the Ancillary Studies Chair is an Ancillary Study co-I for a single-site Ancillary Study, the Ancillary Study PI, or the Ancillary Study Liaison, these responsibilities will fall to the Ancillary Studies Vice Chair for that particular Ancillary Study:

- Assigning two reviewers to each Ancillary Study proposal that comes to the Steering Committee.
- Leading the Steering Committee discussion.
- Writing, or delegating the writing of, the Steering Committee decision/feedback, facilitated by the SDCC's meeting minutes.
- Reviewing revisions to the Ancillary Study proposal and/or protocol, in consultation with the EC, to determine if any significant changes have been made that need to be reviewed by the SC.
- Reviewer pool can be from LCN clinical centers (CC) and may not necessarily be LCN investigators. Each CC can provide a list of qualified reviewers to SDCC and update that list yearly.

5.0 INSTRUCTIONS FOR COMPLETION OF THE ANCILLARY STUDY PROPOSAL FORMS

5.1 Proposal Forms

The Ancillary Study Investigator will work with a dedicated representative from the SDCC to process submissions. All submissions should be sent to lcn@northwestern.edu. See Appendix A for a list of steps in the application process.

Initial Proposal: A one-page proposal summary is required to submit the proposal to the Ancillary Studies Committee. This one-page proposal summary will include: Introductory Information Sheet and One-page Proposal Summary (Appendix C).

Full Proposal: A full proposal and preliminary budget is submitted to the Ancillary Studies Committee once the applicant is invited to submit. The full proposal will include:

1. Introductory Information Sheet and One-page Proposal Summary (Appendix C)
2. Ancillary Study Questionnaire (Appendix D)
    a. Attachment 1: References Cited
    b. Attachment 2: Ancillary Study Draft Consent Form, if additional consent anticipated
    c. Attachment 3: Any proposed questionnaires or forms to be completed by participants (if applicable)
    d. Attachment 4: Ancillary Study Budget (see section 5.2, Budget)
    e. Attachment 5: NIH-style Biosketches of all investigators deemed key personnel

5.2 Budget

The investigator applying for an ancillary study must supply all additional funds needed to complete the study. Provision of funds for expenses incurred by Liver Cirrhosis Network is essential. Once a study concept is approved, the ancillary study team is expected to provide a budget in the full proposal submission, which adequately provides for expenses incurred by Liver Cirrhosis Network. Such may costs include, but are not limited to:

- Statistical and data management staff for coordinating the additional data management and analyses with the SDCC
- sIRB guidance by the SDCC
- Costs incurred by participating clinical centers including space, personnel, equipment, supplies, and sIRB/IRB approval
- Costs for visits outside of the Liver Cirrhosis Network protocols
- Cost of personnel time to pull backup samples
- As appropriate, costs related to participant reimbursement/incentives for their time

6.0 REQUIREMENTS AFTER AN ANCILLARY STUDY IS APPROVED

6.1 Ancillary Study Agreements

The release of data and specimens between sites must adhere to the individual institutional requirements (e.g., data use agreement, material transfer agreements). Any agreements with organizations outside of the LCN, especially industry or individuals, must be reviewed by the NIDDK Technology Advancement Office (TAO) prior to implementation. Network sites and their collaborators will be subject to NIH and IC policies as long as federal funding supported the research activities that led to collection of data and/or biosamples. TAO will ensure that policies are being adhered to and advise the sites' Contract Offices. These policies include, but are not limited to, data sharing, genomic data sharing, and publication.
In the event that biospecimens are sent to an investigator or a third party, all unused biospecimens or leftover biospecimens be destroyed and proof provided to the LCN.

6.2 Progress Reports

The PI of an Ancillary Study will be responsible for providing written progress reports on the Ancillary Study according to the timeline designated by the Steering Committee (typically, annual reports will be required).

6.3 Ancillary Study Papers

Ancillary Studies may not publish data from the Liver Cirrhosis Network study prior to publication of relevant findings from the parent Liver Cirrhosis Network studies. If there are questions about publication timelines, the ancillary study PI should list them in Appendix C under question 6, labeled, “Please list any other comments, questions, or notes you have about your submission.” Exceptions to this policy must be approved by both the Steering Committee and the Publications and Presentations Committee.

Presentation and publication of the results of an Ancillary Study are subject to the same guidelines as all other presentations and publications of Liver Cirrhosis Network (i.e., prior review and approval by the Publications & Presentations Committee before submission of an abstract for a meeting; before presentation of an oral report or poster at a meeting; and before submission to a journal). These should be submitted to Publications & Presentations Committee according to the deadline agreed upon by the Publications & Presentations Committee of the LCN.

Collaborating investigators in Ancillary Studies will prepare papers in cooperation with the clinical centers and the SDCC. Output from data analyses not performed by the SDCC must be provided to the SDCC for review and verification along with the proposed presentation or manuscript. The final text and authorship must be approved by the Publications & Presentations Committee before it is submitted for presentation and/or publication.

All ancillary study data need to be sent to the SDCC within 6 months after the manuscript is approved. The SDCC will provide a secure link to transfer the data files.

Appendix A: Timeline of Ancillary Study Review Process

The applicant should conservatively allow 2-3 months for the review process, prior to submission to the funding agency.

<table>
<tr><th></th><th>Submission</th><th>→ Review</th><th>Timeline</th><th>Notes</th></tr>
<tr><td>Step 1</td><td>One-page proposal to SDCC</td><td>Ancillary studies committee chair + SDCC + Executive Committee as needed</td><td>2 weeks</td><td>The Ancillary Studies Chair, in consultation with SDCC and NIH/Executive Committee, will review the one-page proposal protocol for scientific oversight. Major point to consider in initial review is number of samples/specimens ancillary study requires and whether feasible according to inventory.

If acceptable, invite for full proposal submission.</td></tr>
<tr><td>Step 2</td><td>Investigator invited to submit full proposal</td><td colspan="2">There may be some clarifications on submission, etc. in this process (SDCC and Ancillary Studies chair can help facilitate this).

There is no “official” time limit on submission in general. However, the investigator is encouraged to submit this full proposal within three months of the invitation.</td><td>1. Introductory Information Sheet and One-page Proposal Summary (Appendix C)
2. Ancillary Study Questionnaire (Appendix D)
a. Attachment 1: References Cited
b. Attachment 2: Ancillary Study Consent Form, if needed
c. Attachment 3: Any proposed additional questionnaires or forms to be completed by participants (if different from current protocols)
d. Attachment 4: Ancillary Study Budget
e. Attachment 5: Biosketches of all investigators
f. Attachment 6: Signed agreement stating that the Ancillary Studies personnel agree to abide by Liver Cirrhosis Network policies and procedures</td></tr>
<tr><td>Step 3</td><td>Full proposal</td><td>Ancillary Studies Committee Chair will assign Primary Reviewer and Secondary Reviewer</td><td>2 weeks</td><td>The primary and secondary reviewers will typically be members of the Ancillary Studies Committee. The reviewers may request additional, clarifying information during this time.</td></tr>
<tr><td>Step 4a</td><td></td><td>Executive Committee</td><td rowspan="2">2 weeks – 1 month</td><td>Executive Committee (EC) meets, on average, every week. If received with enough notice prior to the next EC call, it will be included for that week’s discussion. If too close in proximity to next EC call, will either resolve via email or wait until next EC call to discuss.</td></tr>
<tr><td>Step 4b</td><td></td><td>Steering Committee</td><td>Steering Committee (SC) meets monthly. If received with ample time prior to next SC call, it will be included for discussion at that month’s call. If too close in proximity to next SC call, will either resolve via email or wait until next EC call.

SC will vote on decision to not approve / approve / table / request modifications. All decisions will require a majority vote (>50%). Each clinical center has one vote, NIH collectively has one vote, and SDCC has one vote. Members of the Steering Committee who are also part of the Ancillary Study team are allowed to be part of the discussion and vote; however, the Ancillary Study Liaison (and the site which they represent) will recuse themselves of voting.</td></tr>
<tr><td>Step 5</td><td colspan="4">• If approved by SC, SDCC will provide letter of approval on behalf of the LCN SC to the investigators.
• Investigators may use this letter to include in their submissions to funders.
• All approvals are contingent on
(a) the investigator(s) securing appropriate funds to carry out planned studies,
(b) (s)IRB approval,
(c) DSMB approval (as appropriate).
• The above are the responsibility of the Ancillary Study PI.</td></tr>
</table>

Key contacts include: **Ancillary Studies Chair**: Rohit Loomba; University of California San Diego (UCSD); roloomba@health.ucsd.edu; **Vice Chair**: Arun Sanyal; Virginia Commonwealth University (VCU); arun.sanyal@vcuhealth.org; **Scientific and Data Coordination Center (SDCC)**: Northwestern University Data Analysis and Coordinating Center (NUDACC): lcn@northwestern.edu

Appendix B: List of Abbreviations

co-I	Co-Investigator
DSMB	Data and Safety Monitoring Board
IRB	Institutional Review Board
LCN	Liver Cirrhosis Network
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NCI	National Cancer Institute
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institute of Health
NUDACC	Northwestern University Data Analysis and Coordinating Center
PI	Principal Investigator
RCT	Randomized Controlled Trial
SDCC	Scientific and Data Coordination Center
sIRB	Single Institutional Review Board
TAO	Technology Advancement Office
UCSD	University of California San Diego
VCU	Virginia Commonwealth University

Appendix C: Liver Cirrhosis Network Ancillary Study Introductory Information Sheet and One-Page Proposal Summary

Please complete the following items describing the proposed ancillary study and send this proposal to: lcn@northwestern.edu

Key contacts include:

- **Ancillary Studies Committee Chair**: Rohit Loomba; University of California San Diego (UCSD); roloomba@health.ucsd.edu;
- **Ancillary Studies Committee Vice Chair**: Arun Sanyal; Virginia Commonwealth University (VCU); arun.sanyal@vcuhealth.org;
- **Scientific and Data Coordination Center (SDCC)**: Northwestern University Data Analysis and Coordinating Center (NUDACC): lcn@northwestern.edu

Introductory Information

1. Title of proposed study: Click or tap here to enter text.

2. Name of Ancillary Study PI: Click or tap here to enter text.

3. Contact information of Ancillary Study PI:
   Site: Click or tap here to enter text.
   Address: Click or tap here to enter text.
   Phone Number: Click or tap here to enter text.
   Email: Click or tap here to enter text.

4. Is the Ancillary Study PI already affiliated with Liver Cirrhosis Network?

☐ Yes, the Ancillary Study PI is a member of the Liver Cirrhosis Network Steering Committee

☐ The Ancillary Study PI is a Liver Cirrhosis Network co-I, but not a member of the Liver Cirrhosis Network Steering Committee

- Name of the designated Liver Cirrhosis Network Steering Committee Investigator who will act as Ancillary Study Liaison: Click or tap here to enter text.
- ☐ **The Liver Cirrhosis Network site PI at my location has been informed of this proposal, and approves its submission**

☐ No, the Ancillary Study PI is not affiliated with the Liver Cirrhosis Network study

- ☐ An Ancillary Study Liaison has been identified: Click or tap here to enter text.
- ☐ An Ancillary Study Liaison has NOT been identified. The Ancillary Study PI requests that this proposal be circulated among the Liver Cirrhosis Network Steering Committee to request an Ancillary Study Liaison.

5. Select which IRB will be used for this study.
   - ☐ Advarra: sIRB for overall LCN studies
   - ☐ Other, please specify: Click or tap here to enter text.
   - ☐ IRB exemption
     - Briefly explain reason for exemption: Click or tap here to enter text.

6. Names and clinical centers of participating co-Is:
   NOTE: If applicable, include the Ancillary Study Liaison in the list of co-Is. Additionally, if the Ancillary Study PI wishes to use data and/or specimens from a clinical center, the Ancillary Study must include a Liver Cirrhosis Network co-I or site PI from that site as an Ancillary Study co-I
   If available please provide anticipated budget and funding source and whether it is pending or secured.

Co-I Name	Co-I Clinical Center
Click or tap here to enter text.	Click or tap here to enter text.
Click or tap here to enter text.	Click or tap here to enter text.
Click or tap here to enter text.	Click or tap here to enter text.
Click or tap here to enter text.	Click or tap here to enter text.
Click or tap here to enter text.	Click or tap here to enter text.

(Add more lines as needed)

7. Please provide justification for why the aims of the study cannot be accomplished without network resources.
   Click or tap here to enter text.

8. Please list any other comments, questions, or notes you have about your submission:
   Click or tap here to enter text.

One-Page Proposal Summary

Title of proposed study: Click or tap here to enter text.

Describe the background, significance, goals, impact on parent study participants (e.g., samples, procedures), endpoints, and hypothesis/es of the proposed Ancillary Study.
Click or tap here to enter text.

Appendix D: Liver Cirrhosis Network Ancillary Study Full Proposal Form

Please complete the following items describing the proposed ancillary study and send this proposal to: lcn@northwestern.edu

Key contacts include:

- **Ancillary Studies Committee Chair**: Rohit Loomba; University of California San Diego (UCSD); roloomba@health.ucsd.edu;
- **Ancillary Studies Committee Vice Chair**: Arun Sanyal; Virginia Commonwealth University (VCU); arun.sanyal@vcuhealth.org;
- **Scientific and Data Coordination Center (SDCC)**: Northwestern University Data Analysis and Coordinating Center (NUDACC): lcn@northwestern.edu

Title of proposed study: Click or tap here to enter text.
Name of Ancillary Study PI: Click or tap here to enter text.

For Questions 1-10, please limit your response to each question to 500 words.

1. Describe the data to be collected, when those data will be collected (e.g., during each patient visit, at the end of each patient's participation in Liver Cirrhosis Network, after all patients have completed Liver Cirrhosis Network), and the methods to be used for data collection:
   NOTE: If the study involves additional specimen collection, indicate how each sample needs to be processed/handled/shipped, what will be measured in each sample, and the proposed laboratory for the assays/analysis. Also, provide the type and volume for each sample, and the time the sample or samples will be collected in relation to other Liver Cirrhosis Network study procedures. If the Ancillary Study PI requests a current copy of the Liver Cirrhosis Network protocol, please email the Liver Cirrhosis Network SDCC at lcn@northwestern.edu.

Click or tap here to enter text.

2. Indicate which Liver Cirrhosis Network core data are required as part of the ancillary study. If the Ancillary Study Liaison requests a current copy of the Liver Cirrhosis Network Case Report Forms, please email the Liver Cirrhosis Network SDCC at lcn@northwestern.edu.

Click or tap here to enter text.

3. Indicate which Liver Cirrhosis Network resources this study will require, and how the utilization of those resources will be funded.

Click or tap here to enter text.

4. Provide a power analysis justifying the number of participants/samples/etc. to be included.

Click or tap here to enter text.

5. Indicate where the data analyses are to be done and the statistical methods that will be used.
   NOTE: If the Ancillary Study PI requests assistance from a Liver Cirrhosis Network SDCC statistician for study analyses, the budget must include effort for that statistician.

Click or tap here to enter text.

6. Describe the participant burden of participating in the Ancillary Study (the length of time to complete each questionnaire or procedure, etc.).

Click or tap here to enter text.

7. Provide the total number of biospecimens needed by type (e.g., serum, plasma, urine, stool, DNA, other).

Click or tap here to enter text.

8. Describe the study personnel burden (what will the Liver Cirrhosis Network personnel need to do in order to complete the procedures, collect the data, and process the specimens for your Ancillary Study?).

Click or tap here to enter text.

9. Describe the measures taken to ensure participant safety and confidentiality.

Click or tap here to enter text.

10. Are funds available to support this study?

☐ Yes Funding Source: Click or tap here to enter text.

☐ No Proposed Funding Source: Click or tap here to enter text.

11. By selecting the box and submitting this form, you **agree to abide by Liver Cirrhosis Network policies and procedures**, including the Publications and Presentations Policy and the Ancillary Studies Policy. **NOTE:** Data use agreement and material transfer agreements may be needed depending upon the proposal between participating institutions.

☐ **I agree**; Additional comments: Click or tap here to enter text.

Attachments

Please attach the following forms to this proposal submission, and email to lcn@northwestern.edu.

Attachment 1: References Cited

Include an attachment listing the references cited in the proposal. Also include references for the validation and use of the proposed questionnaires (attachment 3).

Attachment 2: Consent Form

If the proposed Ancillary Study requires added consent for any participants, a draft consent form is required as an attachment to the proposal. Participation in the Ancillary Study must be described as optional. Consent for the optional study is only to be sought after the patient has consented to Liver Cirrhosis Network. Consent for Liver Cirrhosis Network is the first priority. Those participants who agree to participate in Liver Cirrhosis Network but do not agree to an Ancillary Study are to remain as Liver Cirrhosis Network participants.

Attachment 3: Proposed Questionnaires or Forms

Attach any questionnaires or forms that will be completed by the study participants. Be sure to cite the validation of each questionnaire in your references (attachment 1).

Attachment 4: Budget

A budget for the proposed Ancillary Study must be attached to the Liver Cirrhosis Network Ancillary Study full proposal. The investigator applying for an Ancillary Study must supply all additional funds needed to complete the study. It is essential to provide funds for expenses incurred by Liver Cirrhosis Network. Ancillary Studies investigators are expected to collaborate with the Liver Cirrhosis Network clinical centers to develop a budget, which adequately provides for expenses incurred by Liver Cirrhosis Network. Such costs include, but are not limited to: statistical and data management staff for coordinating the additional data management and analyses with the SDCC; sIRB costs; costs incurred by participating clinical centers including space, personnel, equipment, and IRB approval; costs for visits outside of the Liver Cirrhosis Network protocol; and personnel costs for pulling backup samples.

The budget should include as much detail as is typically included in an NIH Request for Application proposal submission; namely, if applicable, personnel effort, laboratory analysis, sIRB, shipping, equipment, travel, participant reimbursement, training, etc. costs, broken down by year.

Please submit the budget as a spreadsheet or editable attachment. The SDCC will hide salary information before sending it to be reviewed.

Attachment 5: Biosketch of each Study Team Member considered Key Personnel

Information on creating an NIH Biographical Sketch can be found here:
https://grants.nih.gov/grants/forms/biosketch.htm