

**NASH CRN**

*Nonalcoholic Steatohepatitis  
Clinical Research Network*

**NASH CRN  
Ancillary Studies Policy**

**September 5, 2023**

Table of Contents

1. Background .....	1
2. Definition of an ancillary study .....	1
3. Ancillary Studies Committee.....	2
3.1. Charge of the Ancillary Studies Committee .....	2
3.2. Ancillary Studies Committee membership, election, and voting.....	2
3.3. Ancillary Studies Committee operation .....	3
4. Proposing an ancillary study .....	3
5. Review process for proposed ancillary studies .....	5
6. Funding issues .....	6
7. IRB compliance and proper use of biological specimens and clinical data .....	6
8. NASH CRN general guidelines for access to and use of biological specimens and clinical data.....	7
9. NASH CRN Biospecimens .....	8
9.1. Conditions for accessing NASH CRN Biospecimens.....	8
9.2. Allocation of stored serum, plasma, and DNA biospecimens .....	8
9.3. Disposal of biospecimens remaining at the end of the ancillary study .....	9
9.4. Disposal of NASH CRN biospecimens at the end of NASH CRN funding .....	10
10. Data sharing.....	10
10.1. Provision of the ancillary study data to the NASH CRN .....	10
10.2. Provision of NASH CRN clinical data to ancillary study liaison.....	10
10.3. Sharing of ancillary study data deposited with the NASH CRN.....	11
10.4. Use and destruction of data provided from the NASH CRN DCC.....	11
11. Publications, abstracts, and presentations arising from an ancillary study .....	12
11.1 Publications .....	12
11.2 Abstracts and presentations .....	13
11.3 Authorship.....	14
12. Progress reports .....	15
13. Miscellaneous issues.....	15
13.1. Failure to initiate the ancillary study .....	15
13.2. Amendments to an approved ancillary study research plan.....	15
13.3. Postings to the NASH CRN website .....	15
14. Appendix.....	17

## 1. Background

The Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) studies comprise a large and well-characterized population of individuals with various stages of nonalcoholic fatty liver disease (NAFLD), including steatosis, steatohepatitis, and NASH-related cirrhosis. To make the best possible use of this extraordinary resource, the NASH CRN encourages external investigators, as well as NASH CRN investigators, to develop ancillary studies. Interested investigators must identify a member of the Steering Committee who is willing to oversee the ancillary study and serve as a liaison between the proposer and the NASH CRN Steering Committee.

## 2. Definition of an ancillary study

An ancillary study is defined as a study that uses NASH CRN participants and/or data and biological specimens collected from them for a purpose other than intended by the NASH CRN study scientific objectives as written into its protocols and procedures. In general, ancillary studies are funded by a mechanism that is separate from the NASH CRN funding mechanisms. An ancillary study may require new data or biospecimen collection (i.e., additional to that required by the NASH CRN) from NASH CRN participants, such as a new questionnaire to complete, an additional procedure to undergo, additional blood collection, or additional biospecimens such as urine or stool. If the ancillary study places an additional burden on NASH CRN participants, then a separate consent form is required. An ancillary study may involve all NASH CRN participants or NASH CRN participants at one or several NASH CRN sites. Examples of potential NASH CRN ancillary studies include collecting new, obesity-related data in the NASH CRN population, or using previously-collected biospecimens on NASH CRN participants to run assays on serum and plasma or genomic analyses on DNA.

An ancillary study may not use the central resources of the NASH CRN (e.g., NASH CRN samples in the NIDDK Central Repository, the liver tissue biopsy slide inventory at the Data Coordinating Center (DCC), the NASH CRN digital repository data stored at the DCC, DCC data management resources, or DCC analysis resources) for ancillary study purposes unless such use is agreed upon by the central resource and is entirely supported by the ancillary study. The ancillary study must make its own arrangements for whatever repository, data collection, management, and analysis support that it needs. An ancillary study should not interfere with or significantly overlap with activities of a main study (e.g., PIVENS, TONIC, FLINT, CyNCh, STOP-NAFLD, NAFLD Database, Adult NAFLD Database 2, or Pediatric NAFLD Database 2), a substudy, an existing ancillary study, or a pilot and feasibility study. NASH CRN investigators or liaisons proposing an ancillary study will be required to sign a statement attesting that they have thoroughly reviewed all existing studies (available on the NASH CRN website) for conflict with the proposed study and have identified no conflicts. It behooves investigators and liaisons to find potential conflicts before signing that there are none. If overlap with an existing approved ancillary study is identified, permission to publish all or part of the results from the later ancillary study may be denied.

An ancillary study will be considered complete when the primary results paper for each aim has been accepted for publication. If the approved timelines for completion of the ancillary study are not met (see sections 8, 9 and 10), a formal request justifying continuation of the ancillary study must be approved by the Ancillary Studies Committee.

### 3. Ancillary Studies Committee

#### 3.1. Charge of the Ancillary Studies Committee

The Ancillary Studies Committee is a subcommittee of the NASH CRN Steering Committee. The purpose of the Ancillary Studies Committee is to provide guidance and oversight to the use of NASH CRN resources in ancillary studies (e.g., access to use of existing NASH CRN biosamples, access to NASH CRN participants to collect new data or specimens). The aim is to ensure that NASH CRN resources are used for studies with a high standard of scientific quality that will enhance the overall objectives of the NASH CRN. The charge of the Ancillary Studies Committee is to:

- Develop and maintain policies with regard to proposals of ancillary studies, review and approve study proposals, approve of the use and disposal of biosamples, determine the format of ancillary study data returned to the NASH CRN, and address any other issues related to ancillary studies.
- Assist the Steering Committee by reviewing ancillary study proposals for approval or disapproval. In cases of dispute, or for studies involving large resources of the network, the Ancillary Studies Committee will provide recommendations to the Steering Committee for approval determination by the full Steering Committee, recusing those investigators with a conflict of interest. In the case in which all Ancillary Study or Steering Committee members are included as co-investigators, the final vote is decided by the DCC, the NIDDK, and at least one author not central to drafting the proposal.
- Maintain a list of all proposed ancillary studies indicating approval date and current status of the work (active, completed, disapproved/withdrawn).
- Request status updates from the liaison semi-annually.

The list of all proposed ancillary studies and the list of allocations and commitments of existing or future NASH CRN samples will be available on the closed portion of the NASH CRN website's Ancillary Studies webpage.

#### 3.2. Ancillary Studies Committee membership, election, and voting

The Ancillary Studies Committee has 14 members: 2 co-chairs (one adult principal investigator and one pediatric principal investigator, if possible; appointed by the NIDDK), 8 clinical center principal investigators or co-principal investigators (elected by the Steering Committee), the 2 co-chairs of the Pathology Committee (who share one vote), the Director of the DCC, and the NIDDK representatives (who share one vote). Members will be replaced as needed.

The DCC will coordinate the nomination and election process for the 8 clinical center principal or co-principal investigators. Interested investigators must be willing to attend Ancillary Studies Committee meetings and provide Ancillary Study proposal reviews to keep up with the volume of applications. A ballot will be circulated to the Steering Committee members for an email secret ballot vote. The new members will be decided by a majority vote of the Steering Committee members. In the case of a tie, the Executive Committee will provide a deciding vote.

If an Ancillary Studies Committee member proposes an ancillary study or collaborates on an ancillary study, he/she will be recused from reviewing and voting on that ancillary study proposal, similar to NIH peer review policies, for avoidance of actual or perceived conflicts of interest.

### 3.3. Ancillary Studies Committee operation

The NASH CRN DCC supports the Ancillary Studies Committee's operations. The DCC will: arrange six (6) Committee meetings (usually by conference call) per year, determine new proposal due dates, receive submitted applications for ancillary studies, administer the process for review of submitted applications, write any correspondence for the Committee, maintain the lists of ancillary studies and allocated or committed samples, and archive the correspondence files relating to the Committee's activities. Note that if there are no proposals for review or other Committee business, conferences may be cancelled.

## 4. Proposing an ancillary study

Investigators wishing to conduct an ancillary study must complete a NASH CRN Ancillary Study Proposal (SP) application. The SP form is available on the open part of the [NASH CRN website \(www.nashcrn.com\)](http://www.nashcrn.com), click on Ancillary Studies, then Study Proposal Form). Completed SP forms are submitted to the Ancillary Studies Committee in care of the DCC. Submission of electronically completed PDF forms is preferred over faxed forms for ease of reading; typing the investigator's and liaison's names instead of actual signatures is adequate.

The deadline for receipt of ancillary study proposals for review by the NASH CRN Ancillary Studies Committee is 3 weeks prior to the Committee meeting date (meeting dates are posted on the [NASH CRN website: www.nashcrn.com](http://www.nashcrn.com); click on Ancillary Studies or the Meetings link). Proposals received by the due date without any major issues identified during the initial proposal review by the co-chairs/DCC will be reviewed at the next scheduled meeting. A proposer can request an expedited email review if there is a time-sensitive proposal; however, this decision is at the discretion of the Committee co-chairs.

**Every** ancillary study must have a NASH CRN liaison who is a member of the NASH CRN Steering Committee. The liaison is responsible for 1) proper conduct of the ancillary study, 2) ongoing oversight, and 3) communications with the Ancillary Studies Committee. A link to a listing of NASH CRN Steering Committee members is in the Appendix (section 14).

Investigators who are responding to a program announcement or applying for funding should gain NASH CRN Ancillary Studies Committee approval for the ancillary study **before** submitting their application to a funding organization.

Completion of the Ancillary Studies proposal requires the following information:

- Name of the principal investigator for the ancillary study, his/her institutional affiliation and contact information.
- Name of the NASH CRN Steering Committee member liaison, his/her institutional affiliation and contact information.
- Names of other key investigators for the ancillary study and their institutional affiliations.

- Assurance that all study investigators have reviewed the proposal and agreed to participate **prior** to submission of the proposal to the Ancillary Studies Committee.
- The study title, objective, and estimated start and end dates.
- A concept sheet describing the research design and methods for achieving the study objectives (2- page maximum length - this is to be a concise, well organized description).
- The primary outcome variable and sample size, with justification.
- Specification of the NASH CRN resources which the ancillary study wishes to use:
  - If access to previously collected specimens is required for new measurements, then the quantity and amount of specimens to be used per participant, study and visit must be specified. Note that if exactly 0.5 mL of serum or plasma is needed to run the planned assays, then two aliquots should be requested per participant-study-visit, or the number of assays reduced. Any conditions of specimen collection (e.g., green-top sodium heparin collected blood) must be specified.
  - Number of participants involved.
  - Description of new data or measurements that are to be collected on enrolled or future NASH CRN participants or specimens.
  - If new specimens will be collected, then the quantity of specimens to be collected from participants and the conditions of specimen collection must be specified.
  - Frequency of visits or number of participant contacts for collection of new data or specimens.
  - Types of interview questions, physical measures, or data to be collected from participants.
  - If access to previously collected NASH CRN clinical data is requested (e.g., demographics, previously collected measures on specimens, treatment information), the data items must be specified.
- For biomarker studies, additional information must be included in the proposal as specified in the NASH CRN Biomarker Proposal Guidelines (see link to the Guidelines in Appendix (section 14)). If needed, additional pages may be attached to the proposal.
- The funding source, funding amount, and status of funding for the ancillary study. Any work or personnel time expected of the NASH CRN DCC, investigators or staff that is not reimbursed by the ancillary study must be specified so that the Ancillary Studies Committee can evaluate whether the NASH CRN should assume that unreimbursed work or personnel time or if there will be a fee for the work to be performed.
- If the funding is being provided through a collaboration with industry or another NIH agency (designated as the ancillary study's Collaboration Partner), then the ancillary study's NASH CRN liaison must have a Collaborative Partner Agreement between their institution and the Collaboration Partner, and NIDDK must approve the completed Agreement prior to its execution. The link to the NASH CRN Partner Collaboration Agreement template is included in the Appendix (section 14).
- The status of IRB approval, if separate IRB approval is required, and plans and procedures to protect participant confidentiality.
- An acknowledgment that the NASH CRN Ancillary Studies Policy and the policy on Presentations and Publications arising from ancillary studies have been read and will be abided by the study principal investigator.
- A signed statement attesting that the proposed study has no conflict or overlap with existing studies.
- The date of the expected completion of the assay/genotyping results or other new data once

biospecimens have been received, and the anticipated date of completion of analysis if the study's analysis is performed outside the DCC.

- Any time-sensitive dates for consideration of receipt of biosamples from the NIDDK Biorepository or clinical data from the DCC should be designated by the NASH CRN liaison.

The ancillary study activities that use NASH CRN resources may not proceed until the NASH CRN Ancillary Studies Committee has approved the ancillary study and proof of funding has been received at the DCC.

## 5. Review process for proposed ancillary studies

The DCC will circulate the submitted ancillary study proposal (SP form) to the members of the Ancillary Studies Committee with instructions that they are to send their comments to the DCC by a specified date, typically one week before the meeting or conference call at which it will be discussed. Two NASH CRN investigators will be asked to provide written in-depth reviews prior to the meeting. These investigators do not need to be Ancillary Studies Committee or Steering Committee members. If the proposal is for a biomarker study, a reviewer will be selected from the Biomarker Advisory Committee. If the proposal is for a genetics study, then one reviewer will be selected from the Genetics Advisory Committee upon the advice of the Genetics Advisory Committee chair. The principal investigator of the ancillary study and the NASH CRN liaison will each be notified of the date of the Ancillary Studies Committee meeting in which their study is on the agenda, so that they know the time frame for review. The DCC will collate any comments and distribute to all of the Committee members prior to the meeting.

Upon completion of the discussion and vote of the Ancillary Studies Committee, the co-chairs, with the assistance of the DCC, will prepare a written memo to the ancillary study principal investigator and NASH CRN liaison specifying the Ancillary Studies Committee's decision for approval or disapproval. If the Steering Committee's approval is additionally required, the DCC will distribute the Ancillary Studies Committee's recommendation and decision and put the vote on the next Steering Committee agenda or expedite the vote using a secret email ballot. Following the vote by the Steering Committee, the ancillary study principal investigator and the NASH CRN liaison will then each receive a copy of the memo from the Steering Committee, rather than the Ancillary Studies Committee, specifying the decision for approval or disapproval.

Ancillary Studies Committee members and other reviewers will be asked to assess:

- Whether the study has sufficient scientific merit
- Whether the study has sufficient power
- Whether the study would interfere with other NASH CRN activities
- Whether the study would hamper continued recruitment or participation in the NASH CRN
- Whether the study is consistent with the NASH CRN aim of facilitating a broad range of research relevant to NASH
- Whether the biosample request is justified by the scientific merit of the study
- Whether the volume of requested biospecimens is justified in consideration of other requests for this resource by NASH CRN investigators

- Whether they recommend approval or disapproval of the study
- In addition, the DCC will provide an estimate of the availability of the resource or whether the resource is adequate for the study request

## 6. Funding issues

Ancillary studies must be supported from non-NASH CRN resources. Examples of funding sources include investigator-initiated NIH research grant awards (R01s), NIH program funding awards, grants from local academic institutions or private sources (e.g., drug companies, non-profit health organizations), etc. The NASH CRN Ancillary Studies Committee, on behalf of the Steering Committee, can provide letters of support for applications for funding for ancillary studies approved by the NASH CRN. If funding is not approved, the letter of support may not be used for other applications. A revised ancillary study proposal or amendment should be submitted to the DCC and a new letter of support will be provided. Conduct of ancillary studies must comply with all existing NASH CRN and NIDDK/NIH policies and guidelines.

If the ancillary study applied for funding by NIH or another federal source, any requested NASH CRN data, specimens, and other resources will not be provided until a Notice of Grant Award is issued. If alternative funding is identified, an amendment or revised study proposal form may be submitted that describes the funding and how it will suffice to complete the proposed study.

Services provided by the DCC or other NASH CRN central resource (e.g., additional work from the Pathology Committee), may require payment so as not to draw on existing funding for the NASH CRN. Payment for these services must be funded with non-NASH CRN resources. The investigator may be responsible for costs to the DCC for sample selection, preparation of datasets, and analysis support and advice. Costs, if any, to the DCC or other central resource will depend on the extent of the proposed work, the amount of time estimated to complete the work, and whether the study fulfills a proposed aim of the NASH CRN. The NASH CRN DCC Director and the NASH CRN study liaison, with oversight from the NIDDK NASH CRN Program Official, will determine whether a fee will be charged and the details.

In addition, the study's primary investigator will be responsible for any costs charged by the NIDDK Central Repositories to aliquot, pull, package, and ship requested biosamples. See Appendix (section 14) for NIDDK Central Repositories costs.

## 7. IRB compliance and proper use of biological specimens and clinical data

The NASH CRN liaison to the ancillary study is responsible for ensuring that all uses of any NASH CRN biospecimens or clinical data provided to the ancillary study are in accordance with the consent statements signed by the NASH CRN study participants. Some ancillary studies will require IRB approvals and participant consent statements. The NASH CRN liaison to the ancillary study is responsible for informing the Ancillary Studies Committee (via the DCC) of IRB submissions, amendments, and annual renewals.

Specimens and clinical data provided by the NASH CRN for an ancillary study must only be used for the approved aims specified in the ancillary study proposal. Any new aims will require either an ancillary study amendment or a new ancillary study proposal. Additional information concerning amendments is



provided in section 13.2. Misuse of the biological specimens or clinical data provided by the NASH CRN is a serious breach of academic trust. Consequences will be determined with input from the Ancillary Studies Committee, the Steering Committee, and the NIDDK.

## 8. NASH CRN general guidelines for access to and use of biological specimens and clinical data

Access to NASH CRN biospecimens and data collected on participants will be governed by the NASH CRN Ancillary Studies Committee and administered by the DCC. Biospecimens and corresponding clinical data **are not provided simultaneously**; biospecimens are provided first, and the clinical data will be supplied by the NASH CRN DCC at the time of, or after, completion and receipt of data from the ancillary study. If the ancillary study investigator has requested baseline biospecimens and data from a NASH CRN clinical trial or a study that is still in recruitment and/or follow-up phase, the Ancillary Studies Committee must approve the data/specimen sharing timeline. Otherwise, biospecimens and data will be provided for approved ancillary studies once the NASH CRN study or trial is either complete or the DCC has determined that the baseline or follow-up data are of a quality suitable for sharing, and that the quantity of biospecimens requested does not interfere with the NASH CRN study's aims. Follow-up specimens and associated data and information about treatment assignment in a NASH CRN clinical trial are unlikely to be available until after the NASH CRN trial has ended and the primary paper from the NASH CRN trial has been accepted for publication, regardless of the timing of the submission of the ancillary study. Ancillary study investigators should be aware that there may be delays of possibly years before the requested NASH CRN specimens or data are approved for release to an ancillary study liaison.

The samples and data collected using NASH CRN central resources belong to the NASH CRN. The NASH CRN samples and data are provided to the ancillary study liaison with the understanding that all new data (e.g., biomarker and genomic data) generated through the ancillary study will be shared with other NASH CRN investigators once the primary paper for the primary aim of the ancillary study is accepted for publication. Other NASH CRN investigators may request approval from the ancillary study's liaison for access to a subset of the ancillary study-generated data prior to the DCC release date of the complete ancillary study-generated data file for inclusion in: 1) a NASH CRN manuscript or 2) another ancillary study's analysis. Inclusion of these data will be specified on the publication proposal or ancillary study proposal, which will require review and approval by the Publications or Ancillary Studies Committee (see section 10.3).

The NASH CRN must be granted access to all datasets acquired during the performance of an approved ancillary study prior to presentation or publication of results and upon request.

The clinical dataset will be provided by the NASH CRN DCC at the time of, or after completion and receipt of the generated new data (e.g., genomic, proteomic measures) from the ancillary study. The specified timeline for the receipt of the clinical dataset in relation to the return of the new data should be included in the study proposal, with justification of any special arrangements requested, such as a "new data/clinical data" simultaneous exchange, and approved by the Ancillary Studies Committee. Additional information is provided in Sections 10.2 and 10.3.

## 9. NASH CRN Biospecimens

### 9.1. Conditions for accessing NASH CRN Biospecimens

The NASH CRN biospecimens, e.g., serum, plasma, liver tissue, or DNA samples, will be provided to the ancillary study's liaison only if the following conditions are agreed to in writing by the ancillary study liaison's institution:

- 1) The necessary funding support and availability of staff and equipment to generate the new data are secured and ready to start the ancillary study within 6 months of receipt of the specimens.
- 2) The new data derived from the ancillary study must be completed within 27 months of receipt of the specimens, or 3 months prior to the termination date of the NASH CRN final grant funding cycle.
- 3) Any new data generated by the ancillary study must be sent to the DCC or to an approved designated digital repository **prior to the release** of the clinical dataset by the DCC. Alternatively, the Ancillary Studies Committee, the Steering Committee, and the NIDDK Program Official may approve special arrangements for the provision of the new data with respect to the release by the DCC of the associated clinical data. Arrangements must be included in the ancillary study proposal and/or in the Collaborative Partner Agreement. The NIDDK will oversee the terms of the agreement.
- 4) The ancillary study's liaison and principal investigator must read the Data Sharing requirements designated in the NASH CRN Ancillary Studies Policy and provide assurance to abide by these requirements.

### 9.2. Allocation of stored serum, plasma, and DNA biospecimens

Given the need to preserve serum, plasma, and DNA specimens collected by the NASH CRN, these guidelines will be used by the Ancillary Studies Committee to determine volumes of serum, plasma, or DNA that can be released to investigators for approved ancillary studies.

- 1) Samples available for ancillary studies will be based on inventory reports from the NIDDK Central Repository, as these are confirmed as stored, and reviewed before ancillary study sample selection.
- 2) A minimum of 2 aliquots (1.0 ml) of serum and 2 aliquots (1.0 ml) of plasma on each patient at each study-time point will be retained at the NIDDK Central Repository. A minimum of 1 aliquot containing 5 µg DNA on each patient will be retained at the NIDDK Central Repository. Any use beyond this requires approval by the full Steering Committee and NIDDK.
- 3) Investigators with approved ancillary studies may receive up to 2 aliquots (1.0 ml) of serum, 2 aliquots (1.0 ml) of plasma, or 2 aliquots (10 µg) of DNA on each patient on a "first- come first-served basis." Any request for volumes beyond this requires approval by the Steering

Committee and NIDDK.

- 4) The volume of serum, plasma, or DNA requested must be justified in the Ancillary Study proposal form.
- 5) Special attention will be given to minimizing the use of specimens from key time points such as baseline in all studies, and baseline, anniversary evaluations, and end of therapy from randomized controlled trials.

### **9.3. Disposal of biospecimens remaining at the end of the ancillary study**

It is the responsibility of the NASH CRN liaison for the ancillary study to arrange for proper disposal of any remaining NASH CRN biospecimens after completion of all of the ancillary study aims. Once the ancillary study aims are met, the NASH CRN liaison must submit a plan and timeline for destruction or other disposition of the remaining biospecimens. The plan and timeline must be approved by the Ancillary Studies Committee. Documentation confirming the disposal in accordance with the approved plan must be submitted to the DCC within one month of disposal if the ancillary study liaison does not plan to submit an amendment or a new ancillary study proposal to extend the use of the samples.

Biospecimens received from the NIDDK Biorepository may be kept for a period of up to 5 years from receipt of specimens or up to 3 months prior to the termination date of the final NASH CRN grant funding cycle, whichever comes first. Retention of biospecimens allows execution of rigor and reproducibility requirements and for potential future NASH CRN approved analysis done conjointly only with the NASH CRN. Specimens must be disposed of within 3 months of these dates in accordance with the biosafety committee (or similar agency) of the investigator's institution and meet all local requirements of the institution. Certification of specimen disposal must be provided in writing by the ancillary study investigator and the NASH CRN liaison.

If the primary results of each of the aims of the ancillary study have not been published within 5 years of receipt of the biospecimens, or the termination of the NASH CRN (whichever comes first), then the investigator may request permission from the Ancillary Studies Committee to extend retention of the specimens and to dispose of the specimens at a future date once all aims of the ancillary study have been published. A progress report and proposed timeline for publication will be submitted to the Ancillary Studies Committee along with the written request. The NASH CRN liaison will be responsible for the oversight of the unused biosamples to ensure that the samples are only used for the NASH CRN proposed purpose, and destroyed in accordance with local institutional guidelines.

Specimens cannot be returned to the NASH CRN repository. If, for some reason, the specimens have not been used or are not depleted, and residuals are sufficient to perform additional studies, it is desirable and responsible behavior on the part of the ancillary study liaison and primary investigator to find use for them. Possible uses include additional studies by the investigator or studies by other investigators. Any such use is governed by the NASH CRN in the same way the primary use has been governed. Application must be made for an ancillary study amendment or new proposal by the process described in sections 4 and 13.2. If approval is given to use the remainder of the samples, the NASH CRN takes no responsibility for assuring their distribution or for their quality. Publication of results and other

activities of secondary ancillary studies are governed by the NASH CRN exactly as are activities of primary ancillary studies.

#### **9.4. Disposal of NASH CRN biospecimens at the end of NASH CRN funding**

All biosamples provided by the NASH CRN for an ancillary study remaining at the end of the final NASH CRN funding period must be disposed of 3 months prior to the termination of the NASH CRN as stated in section 9.2. Documentation of biospecimen disposal must be provided via email to the DCC. The ancillary study liaison will be responsible for assuring the destruction of the biospecimens.

Any biosamples belonging to the NASH CRN remaining in the NIDDK Biosample Repository will be documented by the DCC using a random identification number and become available for public use through the NIDDK Central Repository website. The NIDDK Central Repository will provide oversight for the use of these samples, requiring an approved NIDDK Central Repositories Sample and Data Use Certification (SDUC) agreement and a Research Plan for the proposed study and use of biosamples (see Appendix, section 14).

### **10. Data sharing**

#### **10.1. Provision of the ancillary study data to the NASH CRN**

The NASH CRN ancillary study's liaison is responsible for arranging suitable provision of the data files containing the new data (raw or processed assay/genomic or additional data elements) derived from the ancillary study. Suitability of the proposed provisioning arrangements for the deposit in a digital repository (e.g., dbGaP or in the DCC's digital repository) is determined by the Ancillary Studies Committee and the NIDDK Program Official, in consultation with the DCC or other experts who may be designated by the Ancillary Studies Committee or the NIDDK.

The new data derived from the ancillary study must be completed within 27 months of receipt of the specimens, or 3 months prior to the termination date of the NASH CRN final grant funding cycle. If the deadline for deposit of the ancillary study data cannot be met and the NASH CRN is still in operation, then the NASH CRN liaison to the ancillary study may request and justify one extension of no more than one (1) year to submit the new data files. If the final deadline for deposit is not met, the NIDDK NASH CRN Program Official, with advice from the NASH CRN Steering Committee, may require destruction of the data.

#### **10.2. Provision of NASH CRN clinical data to ancillary study liaison**

Once the ancillary study has completed generating new data on any NASH CRN biospecimens provided to the ancillary study and has deposited those new data with the NASH CRN or approved other digital repository, the DCC will provide the NASH CRN clinical data agreed to in the approved Ancillary Study proposal to the ancillary study liaison and to the designated investigator at a collaborating institution. Any designated collaborative investigator is determined by the NASH CRN liaison and must be approved by the Ancillary Studies Committee and the NIDDK NASH CRN Program Officer.

Any new data (raw, processed, or collected) derived by the ancillary study through use of NASH CRN biospecimens or any NASH CRN clinical data provided to ancillary study investigators **may only be used** in the manner specified in the approved NASH CRN Ancillary Studies proposal or in the approved Collaborative Partner Agreement. Any uses not in the approved proposal are subject to prior review and approval of an amended ancillary study proposal. The ancillary study investigators must also comply with applicable data use requirements of the NIDDK and the NASH CRN (see Appendix, section 14, for the template NIDDK Central Repositories Sample and Data Use Certification and the NASH CRN Data Protection Assurance agreements). It will be considered scientific misconduct to use the new data or the shared clinical data from NASH CRN for any purpose other than the purposes specified in the ancillary study proposal aims.

### **10.3. Sharing of ancillary study data deposited with the NASH CRN**

Data that are generated from ancillary studies, such as assay results or genomic data, must be deposited with the NASH CRN. These data may be shared with the NASH CRN investigators once the ancillary study's primary aim has been accepted for publication. However, with express permission by the NASH CRN liaison to the ancillary study, along with the ancillary study's principal investigator, the newly-generated data may be released sooner for an approved NASH CRN publication proposal or for use in another approved ancillary study proposal. The new ancillary study proposal or publication proposal using the new data may not overlap with any other approved ancillary study aim or publication proposal aim. If the study-generated data are used for a new NASH CRN abstract or publication, the ancillary study principal investigator and the NASH CRN liaison will be invited to join the writing committee and included as co-coauthors.

### **10.4. Use and destruction of data provided from the NASH CRN DCC**

Clinical data provided by the NASH CRN for an ancillary study must only be used for the purpose expressly detailed in the proposal or in the Collaborative Partner Agreement. If an investigator discovers a new use for the data, no matter how potentially valuable and timely to an emerging field of study, the liaison must submit either an amendment or a new ancillary study proposal detailing the proposed new use. The amendment or new proposal will undergo full review by the Ancillary Studies Committee. Failure to comply with this requirement will constitute a breach of scientific conduct. The NASH CRN Steering Committee with the NIDDK Program Official will decide on remediation, such as denial of permission to publish the abstract or manuscript or other editorial remedies, such as reporting the breach to the journal and/or to the investigator's institution. Further, no further use of the clinical data will be permitted, and assurance that the clinical dataset has been destroyed will be required.

It is the responsibility of the NASH CRN liaison in collaboration with the ancillary study principal investigator to make a good-faith effort to permanently delete all NASH CRN data files and associated derived electronic data files upon completion of each of the ancillary study aims for which they were acquired. The ancillary study is considered complete when the primary results manuscript is accepted for publication for each of the approved ancillary study aims. Data must be deleted within 2 years of publication acceptance for the last ancillary study aim. Documentation confirming the deletion of all data files must be sent to the DCC within one month of deletion by the NASH CRN ancillary study liaison.

Investigators may request an extension to keep the clinical data for a longer period of time if needed to complete all approved aims. A written request, including the reason for the extension, must

be submitted by the ancillary study liaison to the Ancillary Studies Committee for review and approval. The request must include an assurance that the clinical data will not be used for any purpose other than those specified in the approved Ancillary Study proposal and, if applicable, in the Collaborative Partner Agreement. Any other use of the clinical data for new purposes is prohibited.

For approved extensions that go beyond the termination date of the final NASH CRN grant project funding cycle, the NASH CRN liaison will become the designated Data Custodian for continued approved uses of the NASH CRN data. The designated Data Custodian will provide assurance that the principal collaborative investigator may continue to use but not share the dataset for the approved aims. Any publications arising from the additional aims after the termination of the NASH CRN must acknowledge the NASH CRN investigators via the Credit Roster and also invite the ancillary study liaison and the ancillary study's investigators to be included in the writing committee as co-authors and reviewers. In the case that the NASH CRN liaison can no longer be the designated Data Custodian, then he may designate another co-author who is or was also a NASH CRN Steering Committee member.

## **11. Publications, abstracts, and presentations arising from an ancillary study**

Publications and abstracts arising from ancillary studies must be reviewed and approved by the NASH CRN Presentations and Publications Committee prior to journal or meeting submission. The purpose of the review is to assure that any statements about the NASH CRN protocol are accurate and that the NASH CRN resources used in the ancillary study are appropriately acknowledged. Other purposes are 1) to ensure that no conflict or overlap with ongoing approved ancillary studies or proposed publications exists, 2) that the analysis methods are appropriate to analyze the study proposal's aims, and 3) analysis or validation of the results by the DCC to meet the NIDDK publication reproducibility requirement.

### **11.1 Publications**

The following steps must be completed prior to submitting an ancillary studies manuscript to a journal:

- Send the draft manuscript and author list to the Presentations and Publications Committee in care of the DCC, and specify the target journal.
- An Abstract/Publication Proposal Form (PP) is not required for a publication arising from an ancillary studies proposal; however, the proposal aims must be based on those given in the ancillary study's proposal. Otherwise, an amendment or revision to the ancillary study's proposal must be provided and approved by the Ancillary Studies Committee prior to the manuscript submission to the Presentations and Publications Committee.
- With the assistance of the DCC, the chairs of the Presentations and Publications Committee will identify an internal reviewer for the paper. In addition to the designated reviewer, all Presentations and Publications members are encouraged to provide a voluntary review of the manuscript.
- The reviewer will review the paper for accuracy of statements about the NASH CRN resources used in the ancillary study, for appropriate acknowledgment of the NASH CRN, for overlap with other NASH CRN ancillary studies or publication proposals, and comment on

any concerns about the validity of the data, its analysis, and the conclusions reached.

- The reviewer will send his/her review to the chairs of the Presentations and Publications Committee and the DCC.
- The result of the review may be that the manuscript is approved by the Steering Committee for submission to the NIDDK or that the manuscript needs revisions and further review.
- The final step in the NASH CRN internal review process is submission to NIDDK for review. All papers arising from the NASH CRN, including ancillary study reports, must be reviewed by NIDDK prior to submission. The DCC will submit the manuscript on behalf of the proposing investigator to the NIDDK representatives after receiving approval from the Presentations and Publications Committee. The NIDDK will notify the Presentations and Publications Committee when the manuscript is approved for submission, or if not approved, which further revisions are required for approval.
- If a dispute occurs between the authors of the manuscript and the Presentations and Publications Committee, resolution of the dispute is the responsibility of the Steering Committee. If an irreconcilable dispute occurs over the decision between the lead investigator and the Presentations and Publications Committee, the resolution of the dispute will be determined by a majority vote of the Steering Committee.
- Depending on the disposition of the manuscript after final review, and the advice of the Presentations and Publications Committee, the DCC Director and the NIDDK reviewer, the decision may be that the manuscript may be submitted at the discretion of the NASH CRN liaison and the study's principal investigator, but must use conventional authorship without the approval of the NASH CRN (see section 11.3).

### 11.2 Abstracts and presentations

Abstracts intended for national or international meetings (e.g., AASLD, DDW, EASL) must be reviewed by the NASH CRN Presentations and Publications Committee. The process for review of abstracts will be:

- Draft abstracts based on analysis of an ancillary study must be sent to the Presentations and Publications Committee in care of the DCC **at least 2 weeks** prior to the abstract submission deadline. Note that if the DCC statisticians have not been involved in the analyses, and the planned abstract will be presented "for the NASH CRN," the draft abstract must be submitted **at least 6 weeks** before the submission deadline, along with the analysis plan, tables, and scripts to produce the abstract results. Any abstracts submitted after the due dates cannot be guaranteed to receive the required review prior to submission.
- The abstract will be circulated to the Presentations and Publications Committee for review.
- The results of the review may be that the abstract is approved for submission, not approved for submission, or that it needs revision and a second review by the Presentations and Publications Committee.
- The DCC, on behalf of the Presentations and Publications Committee, will notify the abstract authors of the decision made by the Presentations and Publications Committee and NIDDK before the abstract submission deadline.
- Depending on the advice of the Presentations and Publications Committee, the DCC Director and the NIDDK reviewer, the decision may be that the abstract may be submitted at the discretion of the NASH CRN liaison and the study's principal investigator, but must use

conventional authorship without the approval of the NASH CRN (see section 11.3).

All informal presentations (oral or poster) arising from ancillary studies that are not for national or international meetings will require approval by the NASH CRN liaison and the Ancillary Study co-chairs.

Every presentation from an ancillary study must acknowledge the NASH CRN in the abstract and the in the presentation (oral or poster).

### 11.3 Authorship

Authorship format should be proposed by the ancillary studies writing group and will be subject to review by the Presentations and Publications Committee. Ancillary study abstracts and manuscripts will have either conventional authorship (Name 1, Name 2, ...) or modified conventional authorship (Name1, Name2, ..., for/by the NASH Clinical Research Network). Regardless of the authorship format, the NASH CRN must be identified as the source of the biosamples used in ancillary study. Modified conventional format requires that the data analysis must be either done by the DCC or validated by the DCC. The authorship format must be specified on the Ancillary Study proposal form and, at the time of the initial review by the Presentations and Publications Committee, must be confirmed by both the Presentations and Publications Committee (majority vote) and the NIDDK. ***If conventional authorship:*** 1.) the NIDDK NASH CRN must be acknowledged as the source of the biosamples, taking care not to state or imply that the NIDDK approved the contents of the manuscript; 2.) the NASH CRN investigative group members may be listed as authors only if they participated in the writing of the manuscript; 3.) the SC member who served as the ancillary study liaison will participate in drafting and review of the manuscript and will be a named author; 4.) the NASH CRN DCC must not be acknowledged in the paper, although individual DCC members may be listed due to their contributions; 5.) the NASH CRN grant(s) to the NASH CRN liaison's and the ancillary study principal investigator's institutions must be acknowledged in the abstract/manuscript support statement ; 6.) copies of both the submitted and accepted versions of the paper must be provided to the Presentations and Publications Committee on an informational basis. ***If modified conventional authorship:*** 1.) the NIDDK NASH CRN must be acknowledged as the source of the biosamples used for the paper; 2.) NASH CRN investigative group members may be listed as authors only if they satisfy the authorship requirements in the statement by the consortium of journal editors; 3.) the paper must contain a section, an appendix, or an online supplement crediting the NASH CRN investigators (with institutions and NIDDK NASH CRN grant numbers) who provided the biosamples or other materials or services used in the ancillary study; 4.) the SC member who served as the ancillary study liaison will participate in drafting and review of the manuscript and will be a named author; 5.) the NASH CRN DCC must be acknowledged for provision of the biosamples, their role in the analysis, and, if appropriate, DCC staff may be listed as authors.

If during review of proposed publications an overlap or a conflict with ongoing NASH CRN investigations is discovered, permission to publish will be denied. It may be possible for an author/investigator to resolve the conflict by demonstrating that the results of the study advance the field by improving upon those of existing studies (i.e., an improved methodology was used or additional insights were resulted from the analysis). It is the purview of the NASH CRN Steering Committee to resolve these issues and to oversee how the conflicting or overlapping results are presented in the manuscript in order to maintain the uniformity of NASH CRN conclusions.



## 12. Progress reports

The DCC will query the study investigators and the study liaison of active ancillary studies for a status update semi-annually. Additionally, the ancillary study liaison is responsible for the applicable timely deposits of the ancillary study data to the appropriate public use digital repository (e.g., genomic data results submitted to dbGaP).

## 13. Miscellaneous issues

### 13.1. Failure to initiate the ancillary study

In general, approved ancillary studies must be initiated within one year of being approved or obtaining funding, or the Ancillary Studies Committee may withdraw the approval. The principal investigator of the ancillary study and the NASH CRN Steering Committee liaison will each receive written notice two months before an ancillary study's approval is due to expire. The ancillary study liaison may request an extension. Extensions must be justified and approved by the full Ancillary Studies Committee. The request should include the expected timeline for initiation of the ancillary study and explain the reasons for the delay in starting.

### 13.2. Amendments to an approved ancillary study research plan

If a major change occurs to an approved ancillary study's research plan, the ancillary study liaison must submit an email to the Ancillary Studies Committee describing and justifying the amendment. Changes to an approved ancillary study may include a request for additional samples, adding additional ancillary study aims in alignment with the overall objective of the ancillary study, a change to the Research Plan to use a different method of ascertaining the new data, or a substantive change in the analysis plan. Approval of amendments requires a majority vote of the Ancillary Studies Committee, and, for major amendments, approval by vote of the Steering Committee.

### 13.3. Postings to the NASH CRN website

- Ancillary study meeting dates and proposal due dates for each meeting.
- All study proposals (initial, revisions), reviews, decisions from the Ancillary Studies Committee, and any other material pertinent to the history of the Ancillary Study will be posted on the closed portion of the Ancillary Studies website.
- Final versions of NASH CRN manuscripts arising from an approved Ancillary Study will be posted on the password-protected NASH CRN website Publications page. Slide material prepared for presentations at national or international meetings will also be posted on the NASH CRN website Presentations page.

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### Acknowledgments:

In drafting the NASH CRN Ancillary Studies Policy, we referred to the following sources: Ancillary Studies policies of the Virahep-C, HALT-C, BARC, and CLiC studies sponsored by the NIDDK, and the National Emphysema Treatment Trial sponsored by the NHLBI.



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## 14. Appendix

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- [NASH CRN Ancillary Study Proposal form](#)
  - [Process to obtain NASH CRN biosamples from the NIDDK Biorepository](#)
  - [NASH CRN Steering Committee members](#)
  - [NASH CRN Biomarker Proposal Guidelines](#)
  - [NASH CRN Collaborative Partner Agreement template](#)
  - [NIDDK Central Repositories Specimen and Data Use Certification](#)
  - [Cost of retrieving serum, plasma, liver tissue, and DNA from the NIDDK Central Repositories](#)
  - [NASH CRN Data Use Assurance Protection agreement](#)
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