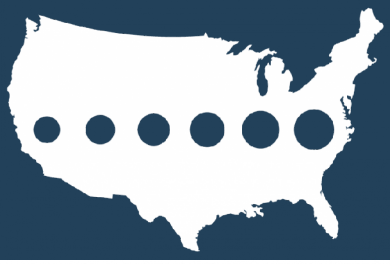

Add Health

The National Longitudinal Study of Adolescent to Adult Health

Ancillary Studies

Researcher Guidelines

Biospecimen Study

UNC | CAROLINA POPULATION CENTER

Biospecimen Ancillary Studies

This document outlines our guidelines and policies regarding biospecimen ancillary studies. Please read and follow the guidelines carefully or your proposal may be returned unreviewed.

A. What is a biospecimen ancillary study?

A biospecimen ancillary study is any study that utilizes archived Add Health biospecimens to conduct new assays and add measures to Add Health that are not included in the activities of the core Add Health Study. Ancillary Study costs are supported by the Investigator and ***must be approved by Add Health before any grants for support are submitted for funding.***

B. The Add Health Biospecimen Archive

Add Health maintains a repository of biospecimens that were collected at various timepoints (Waves) during the study. These biospecimens are finite and have the potential for critical scientific advancement. Add Health has the responsibility of encouraging and supporting ancillary studies that utilize stored biospecimens while also ensuring maintenance of a sufficient biorepository to support future research. For this reason, the Add Health Biospecimen Archive has created two biospecimen reserves: 1) Available for Current Use reserve (also known as Current Use), and 2) Protected reserve. Biospecimen ancillary studies are limited to the Current Use reserve. Further information regarding the two reserves can be found in our biospecimen reserve policy.

When requesting biospecimens for Ancillary Studies, investigators are encouraged to limit their volume requests (including any necessary "dead volume" or padding) to the following. Larger requests must be scientifically justified.

BIOSPECIMEN TYPES, VOLUMES, AND/OR AMOUNTS

Wave	Serum		Plasma		DNA		RNA		Dried Blood Spots		Stool Microbiome		Oral Microbiome	
	n	µL	n	µL	n	µg	n	µg	n	punches	n	volume	n	volume
IV	-	-	-	-	-	-	-	-	4860	7	-	-	-	-
V	4670	250	4576	250	4516	1	-	-	-	-	763	variable	776	variable
VI	5069	250	5052	250	5052*	1	5167	0.5	-	-	1411	variable	-	-

*available in packed cells from which it can be extracted and aliquoted.

Requirements

A. Investigator Requirements

Investigators must meet the following criteria:

1. Have a PhD, MD, or other terminal degree.
2. Hold a faculty appointment or research position at their institution.
3. Work for an institution of higher education, a research organization, or a government agency.
4. Have an institutional review board (IRB) that complies with applicable Federal regulations governing research involving human subjects.
5. Demonstrate completion of research ethics training by all research team members who will work with the Add Health data.
6. Have a demonstrated record of using sensitive data according to commonly accepted standards of research ethics.

B. Costs

Investigators must cover all costs incurred by the study. **Before submitting a proposal for funding from an external agency, investigators must have an approved Ancillary Study and budgets from Add Health and the repository laboratory.** In most cases, investigators will need to establish a subcontract with Add Health and our repository laboratory.

Our biospecimens are archived in repositories in two locations: the Michael Hooker Research Building at the University of North Carolina at Chapel Hill (DBS, stool microbiome) and the Laboratory for Clinical Biochemistry Research (LCBR) at the University of Vermont (DNA, RNA, serum, plasma). Add Health and laboratory staff will work with investigators to develop a budget estimate that includes activities such as sample selection, retrieving samples, processing, shipping, running assays on biospecimens, and other necessary tasks.

Add Health will also conduct quality control, review data for deductive disclosure risk, assist with documentation review and codebook creation, and prepare final files linked to Add Health for dissemination.

Please work with the Ancillary Studies Coordinator to create a cost estimate for your study. This should occur following concept proposal approval and before submission of a full application.

C. Data use and sharing

All biospecimens and any data resulting from biospecimen analysis are the property of Add Health and will be made available to the research community according to the terms of the Data and Material Use Agreement. All data sharing between investigators and laboratories must be done by Add Health.

It is Add Health policy that data resulting from ancillary studies are made available to the Add Health community of data users. Add Health will comply with the data sharing requirements of the funding agency that supports the work, including the funder that supported the original biospecimen collection. All data dissemination is conducted by Add Health.

Add Health does not allow for the commercial use of its data and will not approve ancillary studies that are subject to consulting or licensing obligations to another institution, corporation, or business entity.

D. Ancillary Study process

- Phase 1: Planning
  - Reach out to the Ancillary Studies Coordinator to start planning
  - We recommend that investigators initiate planning for an ancillary study **6 months** before anticipated grant deadlines to allow time for planning, concept proposal, and full application review
  - Determine biospecimen volume needed and sample size
  - Determine laboratory selection
- Phase 2: Application
  - Initial concept proposal and preliminary lab form
  - Budget form for cost estimate
  - Full application
- Phase 3: Funding and agreements
  - Apply for and obtain funding
  - Include ancillary study letter of approval in application
  - Complete necessary agreements, contracts, and approvals
- Phase 4: Conduct your study
- Phase 5: Receive data

Phase 1 - Planning

Before applying, investigators should:

- Contact the Ancillary Studies Coordinator to ask any questions.
- Review previously conducted Ancillary Studies, which are available on the Add Health Website.
- Determine whether the assay(s) can be conducted in Add Health's partner laboratory or will need to be performed by another laboratory. Add Health recommends that testing be conducted at the Laboratory for Clinical Biochemistry Research (LCBR), our partner laboratory at the University of Vermont (UVM). Our Add Health Biology Team has a longstanding working relationship with LCBR, all of our venous blood biospecimens are archived there, and we can best implement all aspects of your biospecimen testing at this laboratory. If an ancillary study requires a specialized laboratory outside of LCBR, investigators must provide justification for this request that includes plans for final disposition of any leftover sample.
- Determine the minimum possible biospecimen volumes needed to complete the proposed work and only request those minimum volumes. Plan to only run samples in singleton.
- Determine sample size. As part of our quality control protocol, we require the inclusion of internal non-participant laboratory controls and participant intra-individual variation (IIV) replicates. Add Health recommends including non-participant laboratory controls totaling a recommended 5% of the participant sample size. Any proposed reduction in the number of quality control biospecimens must be justified in detail at the time of the ancillary study proposal. Add Health will also include approximately 100 IIV samples depending on the type and sample size of each ancillary study.

Phase 2 - Application

Ancillary study applications are reviewed in three steps:

Step 1 - Submit a 1-page concept proposal and preliminary lab form

Concept proposals are reviewed by the ancillary study review committee chair and our central laboratory to determine the feasibility of the study. Applicants are provided feedback and, if approved to proceed, invited to submit a full application.

Step 2 - Submit a budget form

Once the concept proposal is approved, you will need to submit a budget form in order for the Ancillary Studies Coordinator to develop a cost estimate. When preparing the budget, investigators should confirm and include the current cost for preparation and shipping of samples to the testing laboratory being used if other than LCBR. Budget should be included with application submission.

Step 3 - Submit an ancillary study application

After your cost estimate has been prepared, you will be invited to submit a full application that describes the motivation for conducting the project in Add Health, scientific motivation and aims, approach, and timeline. Full applications are reviewed by at least two members of the ancillary studies review committee and our central laboratory.

The review committee will evaluate the following:

- Add Health justification – The proposal should leverage the strengths of Add Health as a nationally representative population-based study of health, and where possible, plan to cover the full sample of available biospecimens at a given Wave. If including all samples in a Wave is not feasible or appropriate, this must be justified. Proposals should be consistent with the policies of Add Health and minimize burden and risk to Add Health participants. The resulting data should add value to the study and benefit the user community.
- Importance of research – What is the significance, rationale, and scientific justification for the study?
- Approach – The scientific quality of the proposed work. Is the approach rigorous and feasible? Can the study be done well in the proposed timeframe?
- Expertise and resources – Are the investigators (and laboratory partners) sufficiently qualified to conduct the study and can their environments support the proposed work?
- Impact on repository – Does the study propose parsimonious use of biospecimens? What impact will the use of the samples have on the remaining volume and sample size available in the Current Use reserve?
- Laboratory justification – If not using our partner laboratory (LCBR), is justification provided? Does the alternate laboratory follow best practices for monitoring and controlling assay data quality, and use conventional tools (e.g., negative/positive controls, calibration standards)?

Add Health welcomes ancillary studies that have scientific merit. However, Add Health will not consider ancillary studies that:

- Duplicate or interfere with existing Add Health activities.
- Adversely affect respondent cooperation in Add Health.
- Threaten the security of Add Health data and/or identities of Add Health respondents.
- Create an unacceptable diversion of Add Health study resources, including personnel or study samples.
- Jeopardize the public image of Add Health.
- Are not consistent with Add Health's scientific objectives.

Outcomes of the review process may be:

- Accept - accepted applications will be provided a letter of approval for their grant application. Investigators should also finalize the budget with the Ancillary Studies Coordinator. Note that ancillary study approval indicates Add Health's agreement to work with study investigators to complete the proposed project, conditional on investigators securing the necessary funding to support the work. Approval does not indicate that investigators have the exclusive right to pursue proposed activities. In some instances, ancillary studies may be proposed and approved that overlap in their planned work. In such instances, Add Health will work with investigators to facilitate collaboration.
- Revise - if revisions are requested, they should be made in a resubmitted application, with tracked changes and comments, along with a response to the changes in a separate document.
- Reject - rejected applications will be provided with a final determination and reason for the decision.

Phase 3 - Funding

Accepted applications will receive a formal written notice documenting Add Health's support for the project and guarantee for collaboration. This notice should be included in any external grant application to fund the project.

After receiving funding, the Ancillary Study Investigator will be required to complete the following distribution agreements prior to the release of any data by the Carolina Population Center (CPC)/University of North Carolina.

1. Review, fill and sign the Data and Material Use Agreement.
2. Apply for a Restricted-Use Contract if one is not already in place by going to the CPC Data Portal.
3. Provide proof of completion of research ethics training by all research team members who will work with the Add Health data.
4. Provide IRB approval for the ancillary study.

Annual Status Reports and Invoicing

After an Ancillary Study is funded and initiated, the PI is responsible for submitting annual progress reports of the study's status to Add Health until Add Health has released final ancillary data. These progress reports must summarize the study's activities, including:

A. Progress of data collected, biospecimens received and lab testing to date
B. Analysis in progress or completed
C. Updates to timeline

Annual report forms will be sent out to investigators no later than June 1 of every year in the study period. These forms must be completed and returned to CPC no later than July 1 of the same year.

Ancillary studies that fail to comply with the annual reporting requirement may be ineligible for renewal of their Add Health restricted-use contract and/or their Data and Material Use Agreement.

The Add Health Studies Coordinator will submit an invoice annually for the work completed during the year. Payment must be received before any data can be released.

Phase 4 - Conduct your Study

As you conduct your study, it is important to communicate regularly with the Add Health team. The Add Health Ancillary Studies Coordinator schedules a kick-off meeting to discuss your study, review the ancillary process and your timeline, and answer any questions.

Study Modifications

After an Ancillary Study is approved, changes in the scope or procedures of the study must be submitted via a modification form, and must be reviewed, and approved by Add Health. Any post hoc changes to approved ancillary study selection criteria, sample size, or protocol must be formally proposed and justified in a modification request submitted to the Ancillary Studies group. Formal review and approval of such requests must precede sample selection. Immediately report any unanticipated changes in laboratory protocol, reagent shortages, substituted materials, or adverse events to the Ancillary Studies Coordinator. A modification form can be found on the Ancillary Studies website or by contacting the Ancillary Studies Coordinator at addhealth_ancillary@unc.edu.

Key Steps

To ensure your study runs smoothly and maintains the highest quality standards, it is essential that the Add Health Ancillary Studies Coordinator is included in your communications with the lab. This inclusion helps us stay informed about the study's progress and prevents any issues with biospecimen tracking or data flow between the lab and your institution. Below is a list of key junctures in which you should speak with the Add Health staff.

Step 1 - Develop a pull list: The Investigator and Add Health work together to create a participant biospecimen pull list based upon approved selection criteria, sample size, and volume.

Step 2 - Masking IDs: Add Health will replace participant IDs with undifferentiated, masked ancillary study IDs before shipping samples to laboratories for assay. Add Health securely and solely maintains the crosswalk between participant IDs and ancillary study IDs.

Step 3 - Send the biospecimens to Ancillary Study lab: Add Health works with the appropriate repository location to send the biospecimens to the laboratory approved for the ancillary study along with a manifest.

Step 4 - Testing and quality control: The laboratory performs testing. When finished, ***the laboratory sends results to Add Health*** along with QC data and internal quality control documentation. Internal quality control documentation should include a summary of procedures and assay data quality (e.g., counts of missing values, differences in/correlations between known and assayed values, coefficients of variation within/between split samples, identification of masked duplicate pairs for studies requesting DNA).

Step 5 - External Quality Control: Add Health assesses data quality based upon the participant, non-participant, and intra-individual variation biospecimens (described in Planning). Add Health will produce an external quality control report that includes standard reliability and validity measures and summary statistics for high-dimensional data.

Step 6 - Receive preliminary dataset: Add Health makes preliminary ancillary study data with temporary ancillary study IDs and quality control documentation available to investigators to assess the data quality and look for errors.

Step 7 - Prepare documentation: The Ancillary Studies Coordinator will provide a User Guide template that investigators will use to prepare the required documentation for the ancillary study data.

Step 8 - Pay invoice: The Ancillary Studies Coordinator will submit an invoice annually for the work completed during the year, and at the end of the work completed. Payment must be received before any data can be released.

Step 9 - Return biospecimens: If applicable, include a return inventory log showing remaining, post-assay biospecimen type and volume and include this electronic document alongside all returned leftover biospecimens to the Add Health biorepository.

Phase 5 - Receive your Data

Upon satisfying the ancillary study protocols, Add Health exchanges the ancillary study IDs for Add Health participant IDS (AIDs), then disseminates the AID-identified participant data to the Ancillary Study Investigator. In order to receive ancillary study data, the investigator will need to apply for a restricted-use data contract. This contract is an agreement signed by two parties, the Ancillary Study Institution and UNC-Chapel Hill on behalf of Add Health. To apply for restricted-use data, please use the Add Health Contracts Management System (CMS) via the Data Portal at https://data.cpc.unc.edu/. There are two types of restricted-use contract options – Secure Research Workspace (SRW) or Home Institution – dependent on your current or intended method of accessing Add Health restricted-use data.

Add Health follows the data sharing policies of the National Institutes of Health that supported the collection of the biospecimens. Under the 2023 Data Management and Sharing Policy, scientific data should be made accessible as soon as possible. Data should be shared by the time of the first associated publication or the end of the performance period, whichever comes first.

Data Security

Protecting the identity of individual Add Health respondents is a critical issue for the Add Health study. Confidentiality of individually identifiable data about Add Health participants must be assured. Unless the approved restricted-use data contract allows otherwise, all data work will take place in the Secure Research Workspace (SRW). The SRW helps keep Add Health data more secure in our efforts to maintain the strict confidentiality of our participants. The SRW is available through remote access. All research and analysis will take place only within the SRW.

Ancillary Study Roadmap

Phase I

- Review Researcher Guidelines
- Review previously conducted Ancillary Studies
- Determine if assay can be conducted in Add Health lab or other
- Determine smallest possible biospecimen volumes needed
- Only request minimum volumes
- Only run samples in singleton

6 months prior to funding submission

Phase II

- Submit one-page concept proposal and preliminary lab form
- Respond to reviewers feedback (resubmit if applicable)
- Submit budget form
- Submit full Ancillary Study application form
- Respond to reviewers feedback
- Receive decision

6 months prior to funding submission

Phase III

- Secure external funding
- Submit additional documentation, including DMUA, ethics training, HIPPA training, and IRB approval
- Apply for restricted-use data contract (if applicable)

Dependent on funding agency's timeline

Phase IV

- Develop pull list
- Testing and quality control
- Evaluate data quality
- Receive preliminary dataset
- Prepare documentation
- Pay annual invoice

Dependent on laboratory

Phase V

- Final data review by Add Health
- Ancillary Investigator is provided exclusive access to the data through the end of the performance period*
- Prepare publications, manuscripts, and presentations using the final released file

6 to 8 weeks prior to exclusive period

*At the end of the performance period, data will be released to the user community.

Add Health

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Please contact and submit applications to:

Email:
addhealth_ancillary@unc.edu

For more information:

Website
https://addhealth.cpc.unc.edu

Address
Add Health
Carolina Population Center
University of North Carolina - Chapel Hill
CB# 8120
Chapel Hill, NC 27599-8120

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