Human Health Exposure Analysis Resource (HHEAR)

Policies for Access to Services
Version 1.3

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1. Introduction and Purpose

The Human Health Exposure Analysis Resource (HHEAR) provides investigators access to laboratory and statistical analyses to add or expand the inclusion of environmental exposures in their research and makes the data publicly available as a means to improve knowledge of the comprehensive effects of environmental exposures on human health throughout the life course.

HHEAR is made up of three main components:

- A Network of Exposure Analysis Laboratories (Lab Hubs), providing access to state-of-the-art technologies for analysis of biological and environmental samples collected from human health studies. HHEAR Lab Hub analysis services are grouped into three broad categories:
  - **Targeted Analysis of Biological Samples:** Analyzing biological samples using a comprehensive suite of targeted, or hypothesis-driven approaches.
  - **Untargeted Analysis of Biological Samples:** Assessing the exposome in biological samples using untargeted, or discovery-driven, approaches, such as metabolomics.
  - **Environmental Sample Analysis:** Analyzing environmental samples such as water, air, and dust using both targeted and untargeted methods.
- The Data Repository, Analysis, and Science Center (Data Center), providing statistical services, a data repository, and data standards for integration and sharing.
- The Coordinating Center, connecting the research community to these analytic resources.

At no cost to investigators, HHEAR can provide a wide range of services, including:

- Expert consultation for your proposed HHEAR project on exposure analysis, study design, and data analysis and interpretation;
- Analysis of human and/or environmental samples using state-of-the-art methods and technologies;
- A data repository and associated data science tools;

- Statistical and data analytical services including support for meta- and pooled analyses; and
- Support for pilot and feasibility studies.

This document was developed for investigators who wish to access HHEAR laboratory and data analysis services.

2. Overview of HHEAR Process

2.1 Application Submission and Review Process

The process to apply for HHEAR services includes a sequence of application submission, consultation, and review steps. An illustration of the key steps and timeline for investigators and HHEAR components is provided in Figure 1. A description of each step in the application review process can be found below and on the HHEAR Public Website (HHEARProgram.org) under How to Apply. Additional guidance on important considerations for submitting a high quality application is provided in the Example Approved Application.

Table 1 presents the deadlines for the application submission and review process. Visit the HHEAR Application Submission and Review Schedule for specific dates associated with the current application cycle deadlines.

Before You Apply

We encourage interested investigators to take advantage HHEAR resources to be fully informed and prepared to comply with HHEAR policies and expectations *before submitting an Initial Application.*

- Go to HHEARProgram.org and review information on HHEAR program goals and research priorities, laboratory and data analysis services, procedures on how to apply, policies, frequently asked questions, and HHEAR research and publications.
- For more information, contact the HHEAR Coordinating Center (CC) at HHEARHelp@westat.com. The CC will:
  - Answer questions on eligibility and policies, and
  - Set up calls with Lab Hub and Data Center scientists, who will provide consultation services on the feasibility of your study design, exposure analyses, biological and environmental samples and data analysis plan.

2.2 How to Apply

Step 1: Create a myHHEAR Account. Your account provides access to the myHHEAR proposal submission and tracking system. To create a myHHEAR account, consult the myHHEAR User Guide.

Step 2: Submit a HHEAR Initial Application. Once you create your account, you can access the Initial Application form online.

Step 3: Initial Assessment. Participate in a call with the Coordinating Center to confirm your eligibility and review HHEAR policies. If you are eligible for HHEAR services, the HHEAR Steering and Executive Committees assess your proposed project for consistency with HHEAR Program goals and research priorities.

Step 4: Consultation and Feasibility Assessment. Consult with one or more HHEAR Lab Hubs and the HHEAR Data Center. The Lab Hub(s) and Data Center will prepare feasibility assessment reports, which document discussions and recommendations, and indicate if your proposed project is feasible.

Step 5: Submit a HHEAR Final Application. The Final Application should address any recommendations made in the feasibility assessment reports. Also, you must submit the appropriate data dictionary, codebook(s), and questionnaire(s) from your parent study. The Lab Hub(s) and Data Center will review these materials to confirm the feasibility of your proposed project.

Step 6: Scientific Expert Panel Review. The HHEAR Scientific Expert Panel will review the Final Application to assess the potential of your proposed project to advance our understanding of how environmental exposures affect human health.

Step 7: Final Decision and Notification. Your funding institution, in consultation with the HHEAR Executive Committee, will make the final decision to approve your application.

2.3 Pre-Tests for Feasibility Assessment

In some cases, HHEAR Lab Hub(s) in consultation with the Data Center and the HHEAR Executive Committee may determine that a pre-test is needed to make a determination of feasibility. For example, a Lab Hub may recommend pre-testing a subset of samples to determine of the exposure of interest can be detected in the samples. The Lab Hub may recommend that the pre-test be completed before the feasibility assessment is decided or alternatively, the pre-test may be conducted after the review process is completed with final approved analyses contingent upon the outcome of the pre-test. Please refer to Appendix 2 for more information about pre-test procedures.

Figure 1. Application submission and review process timeline

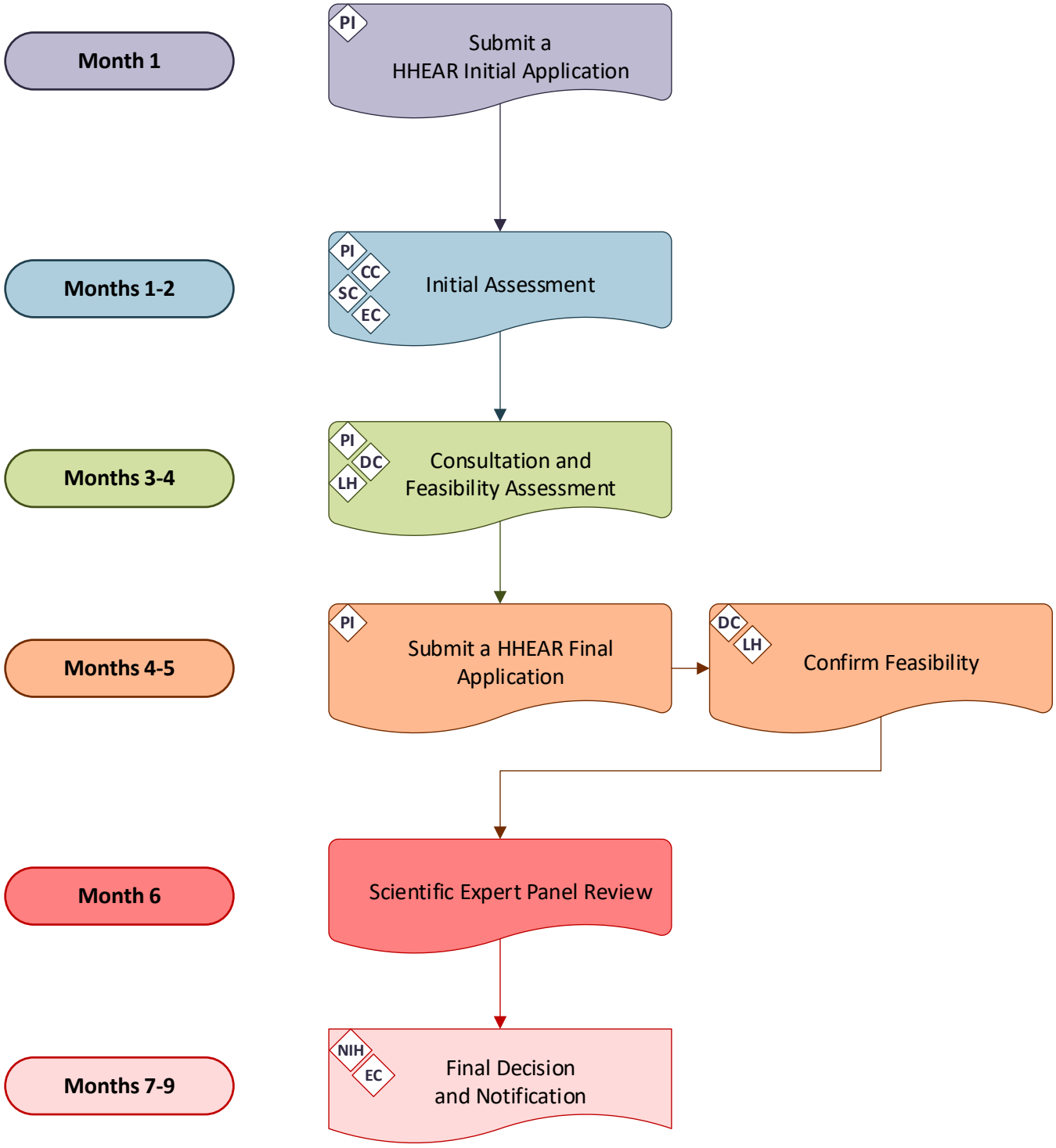

Table 1. Application submission and review deadlines

Step	Task	Responsible party	Approximate Deadlines (Days = Business days)
1	**Create myHHEAR account**	Investigator	Anytime
2	**Submit a HHEAR Initial Application**	Investigator	Continuous, with Initial Application deadline for each review cycle every 3 months.
3	**Initial Assessment** Participate in a call with the Coordinating Center to confirm eligibility and discuss HHEAR policies.	Investigator, Coordinating Center	Complete within 10 days of Initial Application deadline.
	The Steering and Executive Committees will assess your project for consistency with HHEAR Program goals and research priorities.	Steering and Executive Committees	Complete within 20 days of eligibility confirmation and policy review deadline.
4	**Consultation and Feasibility Assessment** Participate in a feasibility assessment call with the Lab Hub(s) and Data Center.	Investigator, Lab Hub(s), Data Center	Complete within 15 days of initial assessment deadline.
	Lab Hubs and DC prepare feasibility assessment reports for investigator.		Complete within 20 days of feasibility assessment deadline.
5	**Submit a HHEAR Final Application** Update as needed, and submit Final Application.	Investigator	Complete within 10 days of receiving feasibility assessment reports.
	Confirm feasibility of proposed project.	Lab Hub(s), Data Center	Complete within 15 days of Final Application deadline.
6	**Scientific Expert Panel Review**	Scientific Expert Panel	Complete within 15 days of Feasibility Confirmation.
7	**Final Decision and Notification**	Executive Committee NIH	Within 60 days of Scientific Expert Panel Review.

2.4 Post-Approval Process

The post-approval process includes all activities to be performed by the investigator and HHEAR components after a Final Application is approved. An overview of the post-approval process is provided below. An illustration of the key steps and timeline for investigators and HHEAR components is provided in Figure 2. The key deadlines for the post-approval process are presented in Table 2.

Step 1: Complete clearance activities. All clearance activities (a-d) must be completed before investigators may ship samples to the Lab Hubs. Activities a, b, and c should be performed concurrently.

a. Upload signed agreements:

- **Institutional Review Board (IRB) Attestation Letter:** Investigators must provide an attestation letter from their institution's IRB confirming that the consent provided by their study participants is consistent with the use of their data, biological and environmental (if applicable) samples for "future unspecified research"; this includes the public sharing of their de-identified data. This approval will indicate that data submission and subsequent data sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained.

- If more than one institution is providing data independently, each institution must provide the IRB attestation letter.

- The HHEAR Program cannot restrict the use of data in the HHEAR Public Data Repository, so we strongly encourage that investigators also review parent study consent forms for all institutions providing data and samples to ensure that the consents allow use of data and samples for unspecified research. **Data Submission Agreement (DSA):** This document outlines the agreement between HHEAR and an investigator regarding submission of data to the HHEAR Data Repository. It must be reviewed and signed by investigators approved for HHEAR services to indicate their agreement to abide by the DSA.

- **Data Sharing Plan (DSP):** This document includes descriptions of: data types; data repositories to which data will be submitted; the timeline for data submission and release; and the appropriate uses of the data. It must be reviewed and signed by investigators approved for HHEAR services to indicate their agreement to abide by the DSP.

- The Data Center will approve signed agreements.

b. Submit **HHEAR Human Material Transfer Agreement (H-MTA)** and/or **Environmental Material Transfer Agreement (E-MTA)**. These documents are used for transfer of human biological materials and environmental samples, with or without accompanying data, between an academic or research (provider) institution and a HHEAR Lab Hub. A HHEAR H-MTA and/or E-MTA must be executed for transfer of biological and/or environmental samples from the investigator's institution to a HHEAR Lab Hub. If samples are sent directly from the investigator institution to multiple HHEAR Lab Hubs, a MTA must be executed for each.

c. Work with the Lab Hub(s) to **complete Lab Analysis Plan(s)**. The Coordinating Center will set up a conference call with you and the Lab Hub(s) to arrange a call to discuss the details of the Lab Analysis Plan(s). The information in the Lab Analysis Plan is referenced in the associated H-MTA or E-MTA and some institutions will require that final Lab Analysis Plans be included with the H-MTA and E-MTA for approval by the institutional representative.

d. After the Data Center approves the IRB Attestation Letter, DSA and DSP, **submit project data to the Data Center:**

- Obtain access to the Data Submission and Review Portal (DSRP). The DSRP is the online application through which participating investigators and Lab Hubs submit their data for analysis and sharing.
- Link to HHEAR Participants IDs (provided by the Data Center).
- Transfer project data to the DSRP.
- The Data Center will approve project data.

Step 2: Prepare and ship samples to the Lab Hub(s). Within 8 weeks after the Data Center approves your epidemiological data, the Coordinating Center schedules a conference call with you to discuss requirements for aliquoting, labeling, and shipping samples. You are responsible for all costs incurred to retrieve, process, and ship samples to the Lab Hub(s).

Step 3: Receive laboratory analysis results files from the Data Center. When the Lab Hub(s) complete the requested analyses, they submit results data to the Data Center. The time to complete the laboratory analyses is dependent on several factors, such as types of analyses, number of samples, and projects already in the analysis queue. The Data Center

reviews the data files and works with the Lab Hub(s) to resolve any problems. The Data Center then notifies you to download the lab results data and summary reports from the Data Center Portal.

Note: All untargeted profiling data is provided to investigators through the Metabolomics Workbench.

Step 4: Receive statistical reports (if requested) from the Data Center. If the Data Center is providing statistical analysis services, they work with you to conduct the analyses and produce reports that enable you to achieve the aims of your HHEAR project. The Data Center notifies you when the final statistical results files for your project are available on the Data Center Portal.

Step 5: Prepare to publish. After you receive lab and statistical analysis results and are ready to prepare your manuscript, refer to the HHEAR Publications Policy for information on determining authorship in discussions with the Lab Hub(s) and Data Center, acknowledging HHEAR in your manuscript, and registering your manuscript with HHEAR.

All de-identified data from your HHEAR project (both epidemiologic data and lab results) are deposited in the HHEAR Data Repository and made available to the public following the data embargo period. For more information about the HHEAR data embargo period, refer to Section 3.3.5 Data Embargo Period of this document.

Figure 2. Post-approval process

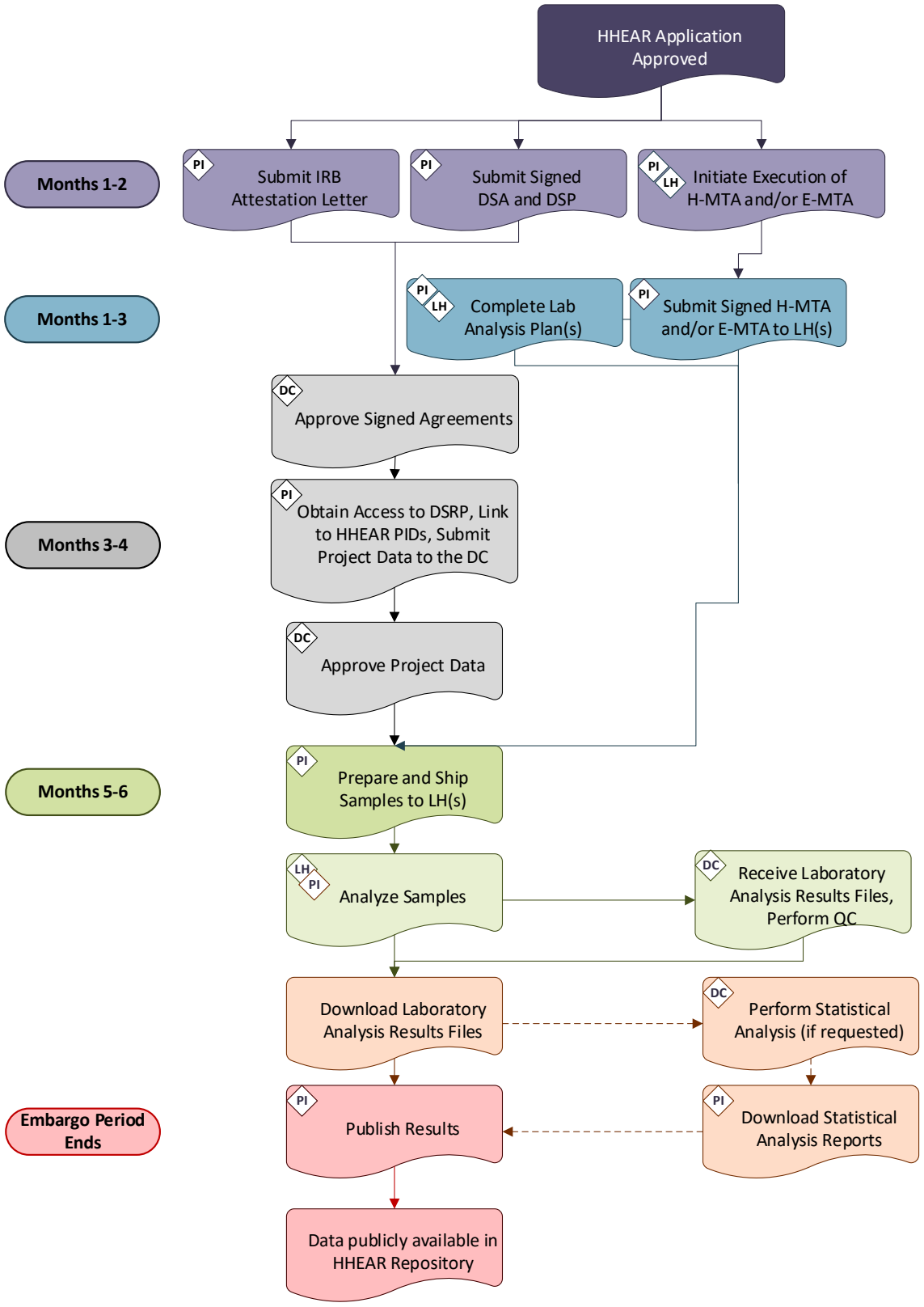

Table 2. Project Post-Approval Deadlines

Task	Responsible party	Deadline
Submit IRB Attestation Letter.	Investigator	Complete within 8 weeks of Final Application approval.
Submit signed DSA and DSP.	Investigator	Complete within 8 weeks of Final Application approval.
Develop Lab Analysis Plans.	Investigator, Lab Hubs	Complete within 8-10 weeks of Final Application approval.
Submit signed MTA(s) to the Lab Hub(s).	Investigator	Complete within 8-10 weeks of Final Application approval.
Data Center approves IRB Attestation Letter, DSA and DSP.	Data Center	Complete within 1 week of document receipt.
Submit project data.	Investigator	Complete within 4 weeks after Data Center approves the IRB Attestation Letter, DSA, and DSP.
Data Center approves project data files.	Data Center	Complete within 2 weeks of data submission.
Prepare and ship samples to the Lab Hub(s).	Investigator	Complete within 8 weeks after Data Center approves project data.

3. Policies for Access to HHEAR Services

The policies governing access to HHEAR services are described below. These policies are intended to ensure the integrity of research supported and conducted by HHEAR and to facilitate the timeliness and quality of HHEAR services. HHEAR requires that investigators document their agreement to comply with HHEAR policies on the HHEAR Initial Application.

3.1 Applicant Eligibility

An investigator may be eligible for HHEAR services if all of the following apply:

1. You have an ongoing or completed epidemiological or clinical study (parent study) with human biological and/or environmental samples linked to health outcome data, and:

    - You want to add environmental exposure data to your parent study or need more extensive analysis of exposures to support a scientific hypothesis related to health outcomes.

    - Although your parent study may be ongoing, you have collected all the data and biological and environmental samples that you will provide to HHEAR for the proposed project prior to submitting your Final Application.

2. You meet at least one of the following funding criteria:

    - Your ongoing or completed parent study is/was funded at least in part by NIEHS extramural funds. In addition, NIEHS will consider support for studies with significant NIEHS engagement that are administered by other NIH Institutes such as the Environmental Health Disparities Centers (administered by NIMHD), the GEOHealth Centers (administered by FIC), and the ABCD study (administered by NIDA) as well as others. Applicants are encouraged to inquire about potential eligibility before submitting an application. Eligible studies supported by NIEHS may request all HHEAR services including targeted and untargeted analysis of biological and environmental samples.

    - Your parent study is/was funded by the NIEHS Superfund Research Program. Studies funded by the NIEHS Superfund Research Program are eligible for targeted and untargeted analysis of biological and environmental samples.

    - Your parent study is currently funded at least in part by NHLBI extramural funds. Studies funded by NHLBI extramural funds are eligible for targeted and untargeted analysis of only biological samples.

    - Your parent study is currently funded by NCI extramural funds and has more than one year of funding remaining at the time you submit the HHEAR Initial Application. Studies funded by NCI extramural funds are eligible for only targeted analysis of biological samples.

    - Your study is an ECHO-wide cohort analysis proposal that has been approved through the ECHO Publications Program, or an ECHO

Opportunities and Infrastructure Fund proposal approved through the ECHO OIF Program. Studies funded by ECHO are eligible for targeted and untargeted analysis of only biological samples.

- ECHO-wide and OIF supported projects are managed through the ECHO program and don't require an additional application for HHEAR services. ECHO cohorts may be eligible for cohort specific analyses through NIEHS, NHLBI, or NCI support through a HHEAR application.

- Email echocc-publications@dm.duke.edu for more information on the ECHO Publications Program. Email echocc-oif@duke.edu for more information on the ECHO OIF Program.

3. You are eligible to apply for an NIH grant at your home institution and you have the authority to commit to documentation such as the MTA, DSA, and DSP.

4. You agree to share your experimental design details and supporting data, including phenotypic data at the individual level, needed to achieve the aim(s) of your proposal.

Investigators must respond to each of these criteria on the HHEAR Initial Application. The Coordinating Center will review each application and contact investigators with any questions.

Non-compliance: If at any time it is discovered that the investigator has not complied with an eligibility criterion, he/she will be asked to submit a Waiver Request Form. The form will include a detailed explanation of reasons for non-compliance. The HHEAR Executive Committee will review the form to determine whether the project must be stopped or can be continued with or without modifications. A list of all circumstances requiring submission of a Waiver Request Form is presented in Appendix 1.

3.2 Scheduling the Consultation and Feasibility Assessment Call

After the initial assessment, investigators will participate in a consultation and feasibility assessment call with one or more HHEAR Lab Hubs and the HHEAR Data Center. The purpose of this call is to provide scientific advice about the Initial Application, including the project's feasibility, overall strategy, methodologies, and analyses.

Due to the complexities of scheduling these calls, timeslots will be pre-specified and assigned on a first-come, first-serve basis. The Coordinating Center will work with investigators to arrange a call from a pre-specified schedule based on the investigator's availability. Investigators are encouraged to be as flexible as possible when assessing their availability to participate in these calls.

Investigators should note that inability to find an agreed-upon timeslot will result in postponement of the Initial Application review to the next review cycle.

3.3 Data Submission and Sharing

After a project is approved and before samples may be shipped to a Lab Hub, investigators are required to submit experimental design details and supporting data to the Data Center. This data will include, but not be limited to, all individual-level project data required to address the project aims. The de-identified project data and associated laboratory results data will be shared publicly through the HHEAR Data Repository. Investigator agreement to submit this data in an eligibility criterion for HHEAR.

Non-compliance: If the investigator is unable to submit all required data, he/she must a Waiver Request Form to submit partial data. The investigator must provide a detailed explanation of reasons for submitting partial data. The HHEAR Executive Committee in consultation with the Data Center will review the form to determine whether the project must be stopped, or can be continued with only partial data submission. A list of all circumstances requiring submission of a Waiver Request Form is presented in Appendix 1.

If the investigator is unable to submit any required data, the project will be stopped.

3.3.1 Assurances and Agreements

Before the Data Center can accept the project data, HHEAR requires the investigator to submit the following assurances and agreements:

- An **attestation letter from the investigator's institutional IRB** confirming that the consent provided by study participants is consistent with the use of

their data, biological and environmental (if applicable) samples for "future unspecified research"; this includes the public sharing of their de-identified data. Often there is a person at the investigator's institutional IRB who is responsible for Institutional Certifications and will be familiar with providing these attestations. An example IRB Attestation Letter is posted on the HHEAR website, under Support Documents.

- Signed **DSA** and **DSP** documents, which indicate investigator agreement to HHEAR conditions for data submission and sharing. Additional information on the policies governing submission of data to the Data Center and the subsequent sharing of data through the HHEAR Data Repository are provided in Sections 3.3.1 through 3.3.5.

Non-compliance: If the investigator is unable to provide the attestation letter and or to provide signed DSA and DSP documents, the project will be stopped.

3.3.2 Authority to Commit to Data Submission and Sharing

In situations where an investigator proposes to use project data from multiple cohorts or a consortium, he/she should identify the individual/institution with the authority to provide the IRB Attestation Letter and sign the DSA and DSP prior to submitting an Initial Application to HHEAR. The investigator must provide contact information on the Initial Application for each individual with the authority to commit to submission and sharing of project data. The Coordinating Center will review each application and contact investigators with any questions.

3.3.3 Deadline for Submission of Assurances and Agreements

The investigator must submit the **IRB Attestation Letter**, **DSA** and **DSP** ***within 8 weeks*** after the investigator is notified of Final Application approval. If all documents are not submitted by the deadline, the investigator will be required to submit an Extension Request Form. The HHEAR Executive Committee will review the form and assign one of the following outcomes:

- The extension will be granted with a condition that the project will be stopped if all of the documents are not submitted by the new deadline; or
- The extension will be denied and the project will be stopped.

A list of all circumstances requiring submission of an Extension Request Form is presented in Appendix 1.

3.3.4 Deadline for Submission of Project Data

The investigator must submit the required project data ***within 4 weeks*** after the Data Center approves the IRB Attestation Letter, DSA, and DSP. The investigator may not ship samples for analysis until after the Data Center has approved the project data.

If the project data is not submitted by the deadline, the investigator will be required to submit an Extension Request Form. The HHEAR Executive Committee in consultation with the Data Center will review the form and assign one of the following outcomes:

- The extension will be granted with a condition that the project will be stopped if the data are not submitted by the new deadline; or
- The extension will be denied and the project will be stopped.

A list of all circumstances requiring submission of an Extension Request Form is presented in Appendix 1.

Investigators should note that extending deadlines will result in delayed services. In some instances, due to capacity issues and project queues at the Lab Hub(s) and/or the Data Center, HHEAR may not be able to guarantee all requested services.

3.3.5 Data Embargo Period

The HHEAR data embargo period is the period during which project data and laboratory results data submitted to the Data Center for an approved project remain unavailable to the public. The HHEAR data embargo period remains in effect until **1 year** has passed from whichever of the following occurs last:

- The date that the final laboratory results data set has been made available to the HHEAR investigator.
- The date that the Data Center returns the first finalized statistical analysis report addressing a minimum of one of the project's specific aims.

Should a manuscript using the HHEAR generated laboratory results data be accepted for publication prior to the end of the defined embargo period, the embargo period will end and all de-identified HHEAR project-related data (both epidemiologic/phenotypic data and lab results) will be made publicly available.

Any deviations from the above policy will have to receive HHEAR Executive Committee approval.

3.3.6 Other Data Sharing Policies

If the investigator is subject to a data sharing policy for his/her parent study, he/she must declare this information on the Initial Application.

3.4 Biological and Environmental Sample Transfer

The following sections provide guidance on HHEAR requirements for biological and environmental sample transfer to HHEAR Lab Hubs and related activities.

3.4.1 Authority to Commit to Sample Transfer

In situations where an investigator proposes to use samples from multiple cohorts or from a consortium, the investigator should obtain permission from each individual/institution with the authority to commit to transfer and use of samples **before** submitting an Initial Application to HHEAR. The investigator must provide contact information for each individual/institution with the authority to commit to transfer of samples on the Initial Application. The Coordinating Center will review each application and contact investigators with any questions.

3.4.2 HHEAR Material Transfer Agreement (MTA)

The HHEAR **H-MTA and E-MTA** are contracts that govern the transfer of tangible research materials between two organizations. The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives. Investigators must submit an

executed HHEAR H-MTA and/or E-MTA for all sources of samples after a Final Application is approved and before samples are shipped to a Lab Hub.

3.4.3 Alternative or No MTAs

It is expected that the HHEAR H-MTA and E-MTA will be acceptable to most institutions. However, when required by the institution, and with the agreement of the HHEAR Lab Hub, the institution's MTA may be used or the investigator may edit the language of the HHEAR H-MTA or E-MTA, provided the HHEAR Lab Hub(s) are in agreement. In order to avoid delays in execution of the MTA at the HHEAR Lab Hub, it is **strongly recommended** that investigators work with institutional authorities to accept the HHEAR MTAs, as written.

Non-compliance: If the investigator or his/her institution is unable to execute the HHEAR H-MTA and/or E-MTA or is unable to execute the HHEAR H-MTA and/or E-MTA without edits, the investigator must submit a Waiver Request Form. The investigator must provide a detailed explanation of reasons that the HHEAR MTA(s) will not be executed. The HHEAR Lab Hub(s), in consultation with the HHEAR Executive Committee, will review the form to determine whether to grant the waiver or stop the project. A list of all circumstances requiring submission of a Waiver Request Form is presented in Appendix 1.

3.4.4 Deadline for Submission of MTAs

The investigator must submit signed MTA(s) for all sources of samples to the Lab Hub(s) ***within 8 weeks*** after the investigator is notified of Final Application approval. If an investigator cannot meet this deadline, he/she must submit an Extension Request Form. The HHEAR Executive Committee will review the form and decide to approve the extension or stop the project. A list of all circumstances requiring submission of an Extension Request Form is presented in Appendix 1.

Investigators should note that extending deadlines will result in delayed services. In some instances, due to capacity issues and project queues at the Lab Hub(s) and/or the Data Center, HHEAR may not be able to guarantee all requested services.

3.4.5 Sample Labeling

Investigators are required to label all biological and environmental samples with HHEAR Sample ID (SID) labels, prior to shipping the samples to a HHEAR Lab Hub. The HHEAR Coordinating Center will provide barcoded HHEAR SID labels.

Non-compliance: An investigator may submit a Waiver Request Form for the sample labeling requirement in a circumstance where **all** of the following criteria are met:

- All samples are labeled in a standard format with a barcode and eye-readable text.
- Labels do **not** contain protected health information (PHI) (e.g., name, participant ID, indication of participant type [e.g., case or control], age, date, gender, date of collection, etc.).
- Each sample vial is labeled with a unique ID.
- Samples do **not** require aliquoting by the investigator prior to shipping to a HHEAR Lab Hub or by a HHEAR Lab Hub prior to shipping to another Lab Hub.

The investigator should include a photograph of the original sample ID label with the form to confirm the exception criteria are met. The HHEAR Lab Hub(s) may request that the investigator provide an example sample vial and label to ensure their laboratory equipment (e.g., barcode scanner, liquid handler, etc.) is suitable for use with the labels. The HHEAR Coordinating Center will review the form in consultation with the HHEAR Lab Hub(s) and HHEAR Data Center to determine if samples do not need to be labeled with HHEAR SIDs. A list of all circumstances requiring submission of a Waiver Request Form is presented in Appendix 1.

3.4.6 Adding Technical Replicates for Lab Analysis

HHEAR recommends that investigators add duplicate samples (also known as technical replicates or split samples) into HHEAR project sample sets before shipping samples to HHEAR Lab Hubs. The number of duplicate samples included in the sample sets will depend on the project size; HHEAR investigators should aim for five percent or 20 samples

as a maximum. Duplicate samples should have their identity masked (i.e., use containers or vials and labeling similar to the HHEAR study sample set).

3.4.7 Costs for Sample Transfer

Investigators are responsible for any costs associated with retrieving samples from storage and packaging and shipping samples to the Lab Hub(s). Investigators may request that a Lab Hub return residual sample volume. The details of this request will be documented in the Laboratory Analysis Plan. Investigators are responsible for shipping costs to return residual samples.

3.4.8 Deadline for Sample Shipment

The investigator must ship biological and environmental samples to HHEAR Lab Hub(s) ***within 8 weeks*** after the Data Center approves project data. If an investigator cannot meet this deadline, he/she must submit an Extension Request Form. The HHEAR Executive Committee will review the form and decide to approve the extension or stop the project. A list of all circumstances requiring an Extension Request Form is presented in Appendix 1.

Investigators should note that extending deadlines will result in delayed services. In some instances, due to capacity issues and project queues at the Lab Hub(s) and/or the Data Center, HHEAR may not be able to guarantee all requested services.

3.5 Changes to Approved Projects

The application review process is designed to facilitate agreement between the investigator and the HHEAR consortium on the HHEAR services to be provided.

An investigator may not make changes to his/her HHEAR project after it is approved without first obtaining the permission from the HHEAR consortium. It is expected that an investigator will take all necessary steps to ensure all information in the Initial Application is accurate prior to submission, and that he/she will repeat this process prior to submitting

the Final Application. It is also expected that the investigator will deliver samples and data for analyses as specified in the report of the approval decision.

If an investigator needs to change any element of the approved laboratory or data analysis, he/she must submit a Project Change Request Form, which includes a detailed description and justification for the proposed changes, and implications for study design and power calculations. The HHEAR Lab Hub(s), HHEAR Data Center, and HHEAR Executive Committee will review the form. In consultation with the HHEAR Lab Hub(s) and HHEAR Data Center, the HHEAR Executive Committee will assign one of the following outcomes:

- The project may move forward with some or all requested changes;
- The project may not be changed, and may continue as originally approved; or
- The project is no longer feasible and will be stopped.

3.6 Publications Policy

The HHEAR Publications Policy provides guidance for assigning authorship and acknowledgement of those who substantially participate in a HHEAR study and the preparation of a publication or presentation. It also ensures accurate reporting of the design, conduct, and analysis of studies, and proper acknowledgement of HHEAR support.

If the investigator is subject to any other publications requirements from collaborators as part of consortia participation, he/she must discuss it with the Lab Hub(s) and the Data Center during the initial assessment. In the event there is disagreement on authorship due to conflicting publications policies, NIH will serve as a neutral third party arbitrator.

The full HHEAR Publications Policy is provided as a separate document.

3.7 Conflict of Interest Policy

HHEAR grantees, including individuals from the Coordinating Center, the Data Center, and the Lab Hub(s), as well as from NIEHS and other funding agencies, are subject to the HHEAR Conflict of Interest Policy. The purpose of this policy is to identify and manage

conflicting relationships, with a goal to preserve transparency, independent decision making, and the integrity of HHEAR research.

The full HHEAR Conflict of Interest Policy is provided as a separate document.

4. Document Control

Revision number	Revision date	Summary of changes
1	February 25, 2020	Updated post-approval processes and eligibility criteria; added links to newly available documents
2	June 15, 2020	Updated sample labeling procedures; updated Appendix 1 for circumstances that may require a waiver; added recommendation to include technical replicates with samples to be shipped for analysis
3	June 2, 2021	Updated timelines for pre- and post-approval processes based on revisions to the proposal review process; made minor editorial changes; added references to pre-test procedures and Appendix 2

Appendix 1

Requests for Extensions, Project Changes, and Waivers

Appendix 1: Requests for Extensions, Project Changes, and Waivers

Form	For	Reviewed by	Outcomes
Extension Request Form	• IRB Attestation Letter • DSA • DSP	Executive Committee	• Extension granted with condition that project will be stopped if all of the documents are not submitted by the new deadline • Extension denied, project stopped
	Project data	• Data Center • Executive Committee	• Extension granted with condition that project will be stopped if all of the data are not submitted by the new deadline • Extension denied, project may move forward with partial data • Extension denied, project stopped
	MTA	Executive Committee	• Approve the extension • Stop the project
	Sample submission	Executive Committee	• Approve the extension • Stop the project
Project Change Request Form	N/A	• Data Center • Executive Committee • Lab Hub(s)	• Project may move forward with some or all requested changes • Project may not be changed and may continue as originally approved • Project is no longer feasible and will be stopped
Waiver Request Form	Eligibility	Executive Committee	• Project must be stopped • Project can continue with or without modifications
	Data submission and sharing	• Data Center • Executive Committee	• Project must be stopped • Project can continue with only partial data submission
	MTA	• Executive Committee • Lab Hub(s)	• Grant the waiver • Stop the project
	Sample Labeling	• Coordinating Center • Data Center • Lab Hub(s)	• Grant the waiver/Use of HHEAR SID labels is waived • Do not grant the waiver/must label sample with HHEAR SID labels.

Appendix 2

Guidelines for Conducting Pre-Tests

Appendix 2: Guidelines for Conducting Pre-Tests

The exposure assays in a Final Application may be contingent upon the results of a pre-test if such test is deemed necessary to determine the fitness-of-purpose of the biological or environmental samples for a proposed HHEAR project. The pre-test may be conducted before the feasibility assessment step is completed or after the review process is completed, but before the post-approval process begins. Guidelines for conducting a pre-test are provided in this Appendix.

1. Conducting a Pre-Test

Step 1: Determine the need and purpose for the pre-test. During a consultation and feasibility assessment with one or more HHEAR Lab Hubs and the HHEAR Data Center, a HHEAR Lab Hub may decide that a pre-test is needed to assess whether biological and/or environmental samples are suitable for the requested analyses and/or whether the analyte selections are appropriate. The Lab Hub may recommend that the pre-test be conducted before concluding the feasibility assessment, or after concluding the proposal review process, in which case, final approval of the proposed project will be contingent upon the outcome of the pre-test.

When a pre-test is recommended, the Lab Hub will provide a **description of the pre-test in the Feasibility Assessment Report**. The description will include the purpose of the pre-test, the samples to be tested, the methods (e.g. lab analysis, checking volume or weight, etc.), results and implications for proposed project if expected results are or are not achieved. This is the minimum information that will be required by reviewers when the pre-test is to be done after the proposal review process is completed.

Steps 2-4 in the process may be conducted before the feasibility assessment is concluded or after the proposal review process is concluded.

Step 2: Design the pre-test. In consultation with the investigator, the HHEAR Lab Hub(s), will complete the design for the pre-test and provide a document to include the following information:

- Number and type of samples to be tested
- Sample selection process
- Indication of whether results will be part of the final data results or whether samples will be rerun with rest of project samples (if project is approved)
- HHEAR QC samples to be included in the pre-test
- Laboratory methods
- Timeline for shipping samples and laboratory testing

The document will be shared with the CC and the DC. It is recommended that the pre-test design should be completed within two to three weeks after it is determined that a pre-test should be done.

Step 3: **Prepare for pre-test**. To complete preparations for the pre-test the investigator will need to determine if his/her institution requires a material transfer agreement (MTA) for transfer of pre-test samples. If an MTA is required the investigator should follow HHEAR procedures to execute an H-MTA or E-MTA. While processing the MTA, the investigator should select the appropriate samples so they can be shipped after the MTA is executed, and as soon as the Lab Hub is ready to receive them. The Lab Hub will provide instructions for shipping the samples. The investigator should inspect the samples before shipping to ensure that no PII is included on sample containers. All samples and any associated data must be de-identified before they are provided to a HHEAR Lab Hub.

It is expected that, if it is required, an MTA will be executed within 8 weeks after the pre-test design is completed, and samples will be shipped to the Lab Hub within two weeks after execution of the MTA. If the MTA is not required, the samples should be shipped within 4 weeks after the pre-test design is complete.

Step 4: Run the pre-test and report results. The HHEAR Lab Hub(s) will conduct the pre-test and compile the results in a summary report. The summary report will include the lab analysis results data, the Lab Hub description of the results and interpretation for the proposed project. The pre-test analyses and preparation of the report should be completed within 8-10 weeks after the samples are received at the Lab Hub.

2. Evaluation of Pre-test Results

Following completion of the pre-test, the results will be evaluated and a decision will be made on next steps for the proposed project. The process for evaluation and decision making is specific to when the pre-test was done, i.e., as part of the feasibility assessment, or after the proposal review process was completed.

2.1 Pre-test with Feasibility Assessment

If a pre-test is done as part of the feasibility assessment, the report of results will be provided to the Executive Committee (EC). The EC will evaluate the report and make a recommendation on next steps for the proposed project. After obtaining recommendations, the Lab Hub will submit a final version of the Lab Hub Feasibility Assessment Report, which will include the results of the pre-test and a recommendation for the Initial Application to move to Final Application with or without changes, or to stop.

The final Lab Hub Feasibility Assessment report should be submitted within 2-3 weeks after the pre-test is completed.

2.2 Pre-test after Proposal Review Process

If the pre-test is done following the conclusion of the proposal review process, the report of results will be provided to the HHEAR EC and the Data Center. The EC will evaluate the pre-test report and make a recommendation to the funding agency IC. The recommendation report will include a decision to approve, approve with modifications, or reject the proposal. Any recommendations for modifications will be clearly indicated as suggested or

required. If modifications are required, the Lab Hubs and the Data Center may be asked to provide information on the implications for updates to the approved analyses, study aims, design or data analysis plan. The IC will make a final decision and the CC will provide the investigator with an updated Final Decision report. The investigator will be asked to provide written agreement to the required recommended changes. The CC will notify the investigator to begin the post-approval process.

The updated Final Decision Report should be provided to the investigator within 4-6 weeks after the pilot test is completed.

3. Submitting Results to the Data Repository

If the final decision is to move forward with the proposed project, the investigator must discuss with the Lab Hub and Data Center whether the pre-test results data will be submitted or samples re-run as part of the HHEAR project.

- If the decision is to not re-run the samples, but to use the pre-test results as part of the HHEAR project, the Lab Hub should submit the results on a modified report template so that the HHEAR Data Center can assign HHEAR SIDs to the results and link SIDs to participant IDs according to information provided by the investigator.
- If the pre-test samples will be re-run, the Data Center will coordinate the labelling logistics with the PI and LH.