

WHI ANCILLARY STUDIES – APPLICATION PROCEDURES GUIDE

The Women’s Health Initiative (WHI) encourages the use of its data through ancillary studies. A WHI ancillary study (AS) is any study that requires the collection of additional data, including data obtained from the analysis of existing biological specimens. The WHI welcomes proposals from investigators within and outside of the WHI organization; studies conducted by non-WHI investigators must include a WHI investigator as a collaborator. Ancillary studies that propose additional characterization of WHI participants should note that direct initial contact of WHI participants must be made through the Clinical Coordinating Center (CCC) or a Regional Center (RC).

All materials related to submission of an application for a WHI ancillary study are available on the WHI website. These materials include:

- WHI Ancillary Studies Policy

Application materials:

- WHI Ancillary Studies - Application Procedures Guide (this document)
- WHI Ancillary Studies - Application Form

Materials for approved Ancillary Studies:

- Ancillary Study Intake Form
- Modification Request Form

Materials for funded Ancillary Studies:

- Data and Materials Transfer and Use Agreement
- WHI Ancillary Study Progress Report Form

WHI DATA AVAILABLE FOR ANCILLARY STUDIES

WHI Questionnaire and Outcomes Data. Refer to the online data dictionary at whi.org for information on data collected during the original WHI study period and collected as part of the WHI Extension Studies. Access to data may require assistance from the sponsoring WHI PI or from the CCC, particularly for multicenter studies or those studies needing data where additional coding is required (e.g., medications). A limited WHI dataset is available by submitting an online application to the [National Heart, Lung, and Blood Institute \(NHLBI\)](http://www.nhlbi.nih.gov); information about this process is available in the Data page of whi.org.

Biological Specimens.

We ask studies to request the total volume that will be required including padding (“dead volume”) at the time they submit their proposal.

Guidelines pertaining to sample volume limits have been put in place in order to conserve valuable biospecimen and are listed on whi.org.

The WHI CCC will add blind duplicate QC samples in addition to participant samples as follows:

10% QC added to the sample size for serum/plasma studies with <1,000 participant samples and all Urine/RBC studies.

5% QC added to the sample size for serum/plasma studies with ≥ 1000 participant samples and all DNA studies.

Requests for modification of blind duplicate numbers will be considered based on QC data from the testing lab for assays being performed (data from vendors will not be considered).

Investigators will not be un-blinded to the identity of WHI blind duplicate QC samples until results are received at the CCC. It is expected that the laboratory include its own QC samples in addition to the WHI blind duplicates. Studies should be designed accordingly for funding and/or supplies.

Whole blood and buffy coat are not available. Once studies are approved and funded, DNA will be extracted and/or serum/plasma aliquots provided by the Specimen and Processing Lab at the Fred Hutchinson Cancer Center (FHCC). The AS Principal Investigator (PI) will be responsible for the associated costs accrued to the WHI, such as specimen retrieval, preparation, and shipping. Once a study is approved by the Ancillary Studies Committee (ASC), AS PIs should contact the WHI CCC Ancillary Studies Coordinator at helpdesk@whi.org to establish the cost figures that may be needed for inclusion in the application for external funding.

REVIEW AND APPROVAL PROCESS

For all proposals: All AS proposals must be submitted to the WHI ASC for approval. Proposals are reviewed for feasibility and scientific merit per National Institutes of Health (NIH) criteria and conformity to WHI mission and policies. Studies that require additional participant consent must also be approved by the Data and Safety Monitoring Board (DSMB).

The ASC forwards approved proposals to the Steering Committee (SC) for their review. Once all reviews and approvals are complete, the SC sends a letter of approval to the AS PI. All letters of support from the CCC are contingent on successful completion of this review process.

For consortium studies: A consortium project is a formalized agreement whereby a multi-study or cohort research project is carried out by two or more academic institutions or performance sites. Prior to the ASC review, the Scientific Resources Working Group (SRWG) will review and conduct initial screenings of consortium proposals to decide if the WHI should participate in an ancillary study. Complete the [WHI Consortium Project Application Form](#). The SRWG will discuss the issue of whether a consortium is needed or whether WHI should answer the scientific question on its own. Review by the SRWG is helpful in providing scientific insights and in making interested WHI investigators aware of the study and thus encourage collaboration and reduce overlap. If the study is approved by the SRWG, they will solicit the Scientific Interest Group(s) (SIGS) to identify a WHI investigator to shepherd the study through the approval process and assure that WHI's scientific and administrative processes are followed once the consortium is underway. This step takes additional time so take this into consideration when planning for ASC review and funding submission.

For proposals requesting biospecimens. Prior to the ASC review, AS proposals requesting biospecimens receive a preliminary review by a CCC Technical Coordinator for participant and

specimen availability, etc., and by the WHI Laboratory Working Group (LWG) for adequacy/relevance of the assay procedures and parsimonious use of biospecimen. WHI seeks a balance between providing sufficient sample for the AS to test the stated hypotheses and the important goal of conserving as much sample as possible for future studies. AS investigators are asked to be explicit regarding their intended assay procedures and willing to consider analytic approaches having comparable results that require smaller volume of specimen.

The amount of biospecimen approved for an AS should be considered the maximum amount approved, subject to reduction at the time specimens are pulled should the LWG determine that assays require less specimen. If the AS PI and the LWG cannot agree on the amount of sample needed for an assay, the AS PI may appeal to the ASC for a final decision.

How to Apply

1. Read and understand the WHI Ancillary Studies policy (located at whi.org).
2. If you are not a WHI investigator, identify a WHI investigator as a collaborator. The WHI collaborator will assist in identifying the information on WHI protocol, measurements and policy, review the specific study plan to assure feasibility of the protocol within the WHI setting, and facilitate access to WHI data once funding is obtained. To obtain help finding a WHI collaborator, contact helpdesk@whi.org.
3. To initiate the ASC review, complete the *WHI Ancillary Study Application Form* and all required attachments (see details below) to helpdesk@whi.org. Page 4 of the application (with the signatures of the sponsoring WHI PI and AS PI) may be scanned and sent as email attachment or faxed to 206-667-4142.
4. Timing of ASC review: The ASC meets monthly by conference call on the third Tuesday of the month. *Proposals must be submitted by the first business day of the month* to be included in that month's agenda. Proposals involving biospecimens will be automatically forwarded to the CCC Data Operations Unit and the LWG for preliminary review at the time they are submitted to the ASC.
5. Since the ASC may have questions or comments and more than one round of reviews may be required, proposals should be submitted to ASC **at least 3 months** before the funding agency's submission deadline. *Consortium studies* may need additional time since it requires review/initial screening by the SRWG prior to submission to the ASC.
6. Approximately one week following the review, the ASC will inform the applicant of the outcome and may ask for additional information/clarification or note provisos. If the AS is approved, studies involving biospecimens will be reviewed by the SC. Following these approvals, the proposal will be forwarded to the DSMB, if required (when there is participant burden).
7. If a study is approved by the ASC, an ASC approval letter will be sent. This letter will include the name of a CCC Administrative Project Coordinator who should be contacted to discuss the CCC work scope and determine if a subcontract is needed. If a CCC subcontract is needed, the *WHI Ancillary Study Intake Form for CCC Participation* is to be completed.
8. Once application has been approved at all stages, a notification of approval will be provided by the SC.
9. Submission for funding can occur upon receipt of approval from the SC.

Application Proposal Format

A narrative/cover letter describing the AS proposal should be included with the *WHI Ancillary Study Application Form*. In addition, if the AS requires a consent form, it should also be included with the application. Note that the consent form must clearly indicate that participation in the AS is a separate activity that will not affect the woman's participation in the WHI in any way.

The format of the proposal should largely conform to the NIH grant application specifications (SF424/PHS398) (www.nih.gov):

- Maximum of 12 pages (including abstract, tables and figures); references may be additional. Please be as concise as possible; proposals exceeding 12 pages will be returned for editing.
- Use an *Arial, Helvetica, Palatino Linotype or Georgia typeface, a black font color, and a font size of 11 points or larger*. A symbol font may be used to insert Greek letters or special characters; the font size requirement still applies. The application must be single-sided and single-spaced. Consecutively number pages.

To ensure an efficient review process, include the following in your proposal (while staying within the 12 page limit):

- (a) A 200-300 word abstract communicating the key objectives. This abstract should summarize the background, aims, and methods, including basic design (e.g., case-control, cohort, randomized trial), study population (e.g., OS, CT, HT, DM, CaD, WHIMS, AS97), sample size, specimen requirements (e.g., .1 ml at baseline and year 3), if applicable.
- (b) Specific Aims
- (c) Research strategy, including Significance (particularly in contributing to the health of post-menopausal women); Innovation; Approach
- (d) Approach includes (as applicable)
 - Overall strategy and Methodology
 - Data collection and details of data pooling (e.g., in consortia) including comparability of data, decision making and publication issues
 - Statistical design, analyses, and power calculations
 - Potential problems, alternative strategies and benchmarks for success anticipated to achieve the aims
 - Confidentiality
- (e) Rationale for WHI resources - Specify how the proposal draws on unique features of WHI
- (f) Investigator qualifications and involvement in WHI
- (g) Environment

Resubmissions and Modifications

Resubmissions: If the ASC or SC has too many concerns to approve a proposal they may request that it is revised and resubmitted. You will receive a letter with reviewer comments and a list of required or recommended actions (if applicable). Send your resubmission to helpdesk@whi.org and include (1) a cover memo addressing the concerns and explaining any changes made to the proposal, (2) a signed revised AS application form, and (3) both a clean and tracked version of the revised proposal.

Modifications: Any changes to an ASC approved study require a modification (see the [AS Policy](#) for details). If you need to make changes to your ASC approved study, submit to helpdesk@whi.org (1) a new [ASC modification form](#) including rationale for proposed changes and (2) both a clean and tracked version of the revised proposal.

Additional information needed for AS requesting biospecimens:

- (h) Express amount of specimen requested as follows (it is imperative to justify sample size and amount of specimen requested, including padding):
 - Serum, EDTA plasma, citrate plasma, packed RBCs, and/or urine in μ l
 - DNA in μ g
 - RNA
- (i) List genes to be studied by gene name followed by HUGO Gene Nomenclature Committee gene symbol in parenthesis, e.g., low density lipoprotein receptor (LDLR), estrogen receptor 1 (ESR1). (If you do not know the gene's symbol, see <http://www.gene.ucl.ac.uk/nomenclature>.) For studies of specific SNPs, include the RS numbers. For GWAS and multiplexed assays, include the Platform name and version number.
- (j) In the Methods section, include laboratory methods (i.e., be specific about analytes, assay methods, minimum sample volume required, and assay validity/reliability measures).

WHI PUBLICATION POLICIES

The WHI Publications and Presentations (P&P) Committee has policies for manuscripts and reports of data resulting from ancillary studies, available at www.whi.org.

Proposals and analysis plans for manuscripts and abstracts that will report findings from ancillary studies must be reviewed by WHI P&P and NHLBI before the CCC can release the corresponding WHI data needed for the ancillary study analysis. In addition to a proposal, studies involving biospecimens must submit their assay results before the CCC can release the additional data needed for analysis. Therefore, AS investigators are encouraged to submit a proposal to the P&P committee shortly after the funding period starts to ensure timely access to WHI data.

Please contact the helpdesk@whi.org with any questions about this process.