WOMEN'S HEALTH INITIATIVE
ANCILLARY STUDIES POLICY

A Women's Health Initiative (WHI) ancillary study (AS) is an investigation that involves generation of new data not already in the WHI database. Examples include:

- Abstraction of records previously collected by WHI but not yet coded (e.g., four-day food records, medical records)
- Specimen assay results
- Collection of new survey data or clinical data

Some studies only generate new variables that are constructed from existing WHI data; such studies are not considered WHI ancillary studies.

AS require outside (i.e., non-WHI contract) funding.

Investigators are encouraged to propose and conduct AS. Such studies enhance the value of the WHI and promote the continued involvement of a diverse group of investigators, which is critical to the success of the study.

To protect the integrity of the WHI, AS must be reviewed and recommended for approval by the Ancillary Studies Committee (ASC) and the WHI Steering Committee (SC). Studies requesting access to biological specimens or those involving informed consent require additional levels of review (described in detail below). Maintaining the integrity of the WHI, retaining study participants, and adhering to the WHI protocol are of paramount importance; any proposed AS that would interfere with WHI procedures, involve unreasonable participant burden, or possibly lead to participants leaving the study early is unlikely to be approved.

Recruiting and Consenting WHI Participants to Ancillary Studies

Generally speaking, any WHI participant may be recruited for an approved AS. In addition to the ASC, and SC, the Data and Safety Monitoring Board (DSMB) will review ancillary studies that propose to contact participants to ensure that participant burden is reasonable and there is no conflict with established WHI objectives.

Any AS involving recruitment of WHI participants is to be introduced to the participants by the local WHI Regional Center (RC) Principal Investigator (PI) or by the WHI Clinical Coordinating Center (CCC), and must clearly state that participation in the AS is a separate activity that will not affect a woman's participation in WHI.

WHI PI and CCC Participation in Ancillary Studies

A WHI PI must be included as a sponsor in every AS proposal; however, co-investigators named on a WHI RC or CCC contract may propose an AS without a PI sponsor.

All AS involving multiple sites or using WHI biospecimens must also involve the CCC for purposes of data coordination and/or coordination of biospecimen transfer, unless the CCC deems this unnecessary. Any AS that may possibly involve any type of CCC support, such as studies involving multiple sites, participant recruitment, or biospecimens, is advised to discuss a budget with the CCC administrative coordinator before submitting funding requests, or risk the possibility of the CCC being unable to provide the necessary level of support once the study is funded.

Access to Biological Specimens

Access to biological specimens (biospecimen) for AS is managed by the ASC and CCC through the application process described below. Guidelines pertaining to sample volume limits have been put in place in order to conserve valuable biospecimen and are listed on our website (https://www.whi.org/researchers/SitePages/Specimens%20Available%20for%20Proposed%20Studies.aspx). Parsimonious use of specimen is an important consideration in review of AS proposals.

The ASC will consider proposals requesting sample volumes larger than the posted guidelines. To be approved for higher amounts, scientific justification must be included in the proposal, and a copy of the assay procedure(s) provided. Biospecimen volumes approved by the SC will be re-evaluated by the CCC at the time of funding and may be revised to meet current technology.

Please note that sample volume requests must include any necessary 'dead volume' padding.

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.

To ensure that WHI biospecimens are being used for investigation of the most current and relevant hypotheses, approval for each AS involving biospecimens will be in effect for 30 months from the date of the approval letter from the PO. The CCC will not support funding submissions past 21 months as they are unlikely to result in funding by the 30th month expiration date. If a PI does not secure funding but would still like to pursue the study, they are welcome to re-apply to the ASC for approval.

Biospecimens must not be used for any purpose other than what they were approved for. If a PI wishes to use residual specimens for additional assays, approval must be granted by the ASC. WHI does not accept unused portions of biospecimens back into the biorepository.

DNA Extraction by Other Groups

DNA extraction will remain primarily at the Fred Hutch specimen processing lab (SPL) to maintain comparability, consistency, quality, and integrity for all WHI studies. Under certain circumstances DNA could be extracted at other labs. The WHI LWG will evaluate such requests on a case-by-case basis. Factors that would need to be evaluated in considering an exception to the current policy include DNA quality, cost, timeliness, etc., of the newly proposed lab, comparability of extraction procedures with SPL, or the need for alternate extraction procedures, and confidence in the integrity of the lab (e.g., for returning all remaining, appropriately labeled samples). The LWG would be responsible for the identification and evaluation of the technical requirements for DNA extraction by outside labs.

Access to WHI Data

Access to WHI data sets on http://www.whi.org/researchers/data/Pages/Home.aspx is restricted to the following investigators:

- Current WHI PI
- Former WHI PI who was active during the first WHI Extension (2005-2010) for at least one year
- Lead author on an approved paper
- AS PI*

* For a PI of a non-biospecimen AS to gain access to the WHI data, he/she must have an approved paper proposal and return a signed copy of the WHI Data Use Agreement (DUA) to the WHI Helpdesk. The PI of an AS using biospecimen has the additional requirement of submitting the biospecimen test results to the WHI CCC prior to gaining WHI dataset access.

Funding for Ancillary Studies

All AS require funding from non-WHI contract funds. WHI SC approval of an AS is required prior to submission for funding.

If an AS requires WHI specimens, recruitment, or consent from more than one RC, a subcontract with the CCC is required. The budget for the subcontract must be prepared by the CCC prior to funding submission.

Application and Approval Process

Detailed application instructions can be found at: https://www.whi.org/researchers/SitePages/Ancillary%20Studies%20Overview.aspx. To initiate the review process, investigators must complete the *WHI Ancillary Studies – Application Form.* Once submitted, AS proposals will be forwarded to the appropriate review committees, described below.

Scientific Resources Working Group (SRWG) Review *(for consortium studies only).* The ASC Chair presents the consortium application to the SRWG for review of the project's impact on WHI resources, contribution to WHI's scientific goals, whether or not WHI could meet the project's goals without participating in the consortium, and the overall feasibility of the project. For projects recommended for further consideration, the SRWG identifies one or more WHI Scientific Interest Groups (SIG) to discuss the proposal. When approved, a consortium sponsor is assigned. The sponsor will advise on scientific matters and shepherd the study through the WHI administrative process once the consortium is underway. Refer to our website for Consortium Project Guidelines and Procedures for the WHI**.**

Laboratory Working Group (LWG) Review *(for biospecimen studies only).* Studies requesting access to biospecimens are initially reviewed by the WHI LWG. Review of biospecimen studies involves assessing feasibility (i.e., availability of requested specimen by outcome category), efficient use of specimen, impact on the biorepository, quality control matters, and compatibility with the current portfolio of WHI core biospecimen studies and approved ancillary studies.

ASC Review *(for all studies)*. The ASC reviews each AS proposal per NIH criteria, WHI priorities and policy, and operational criteria, including acceptable informed consent and burden on WHI participants, if applicable. While in-depth, NIH-style review is not the primary purpose of this

review process, the ASC provides a general scientific appraisal of all ancillary studies. The ASC takes into consideration the SRWG and LWG recommendations.

If the ASC does not approve a proposal, the PI will receive detailed feedback and is welcome to resubmit the proposal with a response addressing the reviewers' concerns.

WHI Steering Committee (SC) Review *(for all studies)*. The SC only reviews AS proposals that have been approved by the ASC. The SC takes SRWG, LWG, and ASC comments into consideration and votes to recommend final approval. The proposal is reviewed by the SC to confirm that the proposed AS will not compromise, complicate, or jeopardize the conduct of the WHI.

Data and Safety Monitoring Board (DSMB) Review *(for studies involving participant contact)*. Studies involving separate consent and/or additional participant burden must also be reviewed by the DSMB. If a DSMB review is needed, it is facilitated by the NHLBI Project Office (PO) and approval is communicated in an SC letter. PIs must complete the *DSMB Participant Burden Summary Form.*

Modification of Approved Ancillary Studies

Any proposed changes to the design of an ASC approved AS, including changes in sample size, biomarkers, or use of specimens (including use of residual specimen), must be approved by the ASC. Modifications involving an increase in sample size greater than 10% and/or a change in specific aims are required to go through the entire review process (LWG, SC, NHLBI) again. If the proposed change will significantly add to participant burden or raises new human subjects issues, the modification must also be approved by the DSMB and NHLBI PO. To be considered in the study's funding submission, AS PIs need to allow sufficient time for review of the requested modifications before funding submission deadlines.

Analysis and Data Ownership

Upon study funding, WHI and the AS PI will sign a Data and Materials Transfer and Use Agreement (DMTUA) outlining the data and/or biological specimens to be released to the PI and the relevant WHI policies with which the PI agrees to comply.

Data of any kind generated by an AS (e.g., biospecimen assay results, new FFQ variables) are required to be submitted to the WHI CCC. For studies testing WHI biospecimen, the test results must be submitted to the CCC before the AS PI is granted access to the WHI investigators' dataset. For all studies, WHI requires that the following be submitted to the CCC at the time of the primary publication from the study: a final analytical dataset that includes data generated from the AS, a data dictionary, a one page summary of the results, and updated PI contact information.

One year after the study's funding end date and without notifying the study's PI, WHI may release data generated by the AS to qualified scientific investigators requesting access through established WHI procedures. WHI will encourage the scientific investigators requesting access to collaborate in analyses and publications with the PI who generated the data.

Studies with Industry Involvement

There are a number of different scenarios involving ancillary studies and industry:

- Investigator initiated study with industry funding but no scientific involvement from industry
- Industry funded study with industry involved as co-investigators
- Federally funded study supplemented with industry funded assays.

Depending on the industry involvement, the selection pool may be limited to include only those women that have consented to commercial use of their data and/or specimens.

It is a requirement that NHLBI review the Collaborative Research Agreement (CRA) between industry and AS PI prior to WHI approval. In addition, any industry investigators will be required to sign the WHI DMTUA and DUA.

If the study is a genetic study, the PI is required to submit results to dbGaP even though the AS is not funded by NIH, as the resource being used is a publically funded resource.

Depending on current workload at WHI, specimen processing may need to be limited to no more than one half of the total WHI pipeline capacity.

Limited Datasets for Industry Investigators

Industry partners have limited access to the WHI Investigator website. In particular, data security and integrity will be provided whereby industry partners will be given a specific dataset suitable for the specific hypotheses proposed that have been approved (either by P&P as manuscript proposals or ASC as ancillary studies). This is in contrast to WHI investigators (from academic, governmental, or non-for-profit organizations) who are given permission to access the WHI databases and download data themselves. Industry partners can make additional data requests if they have another legitimate hypothesis that is approved by ASC or P&P.

This process would help to withstand any potential risks coming from all directions or potential findings that may get misinterpreted. Finally, industry partners should understand that only a portion of the WHI participants gave permission for data and biospecimens to be utilized by commercial entities.

The costs for preparing the datasets is to be determined as it may fall outside the CCC contractual arrangements.

Database of Genotypes and Phenotypes (dbGaP)

For those studies that submit data to dbGaP, the Ancillary Study PI is responsible for the institutional certification, study registration and data submission. Per NHLBI policy, Investigators must register their data on dbGaP as a substudy to the parent WHI Study (phs000200) to ensure the proper data use limitations and consent groups apply. WHI data must be submitted under consent groups Health/Medical/Biomedical-IRB and Health/Medical/Biomedical-IRB-NPU. The process is complicated, so the WHI CCC has developed guidelines that can be found at https://www.whi.org/researchers/SitePages/Ancillary%20Studies%20Overview.aspx.

Annual Progress Report

The PI of each AS is expected to submit a written progress report to the CCC and ASC annually, using the WHI Ancillary Study Progress Report Form.

Publications and Presentations

Publications resulting from an AS must follow the policies described in the WHI Publication and Presentation (P&P) Policy, which is available on our website: https://www.whi.org/researchers/SitePages/Write%20a%20Paper.aspx . All publications and presentations involving WHI study data are to be submitted to the WHI P&P Committee and the NHLBI PO for approval prior to submission to the target journal. Proposals and analysis plans for manuscripts and abstracts that will report findings from ancillary studies must be reviewed by WHI P&P before the CCC can provide access to the corresponding WHI data needed for the AS analysis.