Guidelines for Use of Survey and Clinical Data Collected in the
Shanghai Women’s Health Study

A. Submitting a Research Project Proposal

1. Any investigator wishing to develop a collaboration with the Shanghai Women’s Health Study (SWHS) investigators to use SWHS data should first submit a detailed proposal via the SWHS website. The format of the proposal is described in detail below.

2. The proposal's format is similar to an NIH grant (i.e., specific aims, background and significance, preliminary studies, and methods) but should be no longer than 6 pages in length. The proposal should also include required variables and justification for using the SWHS resources. The reasons for proposing use of SWHS data, rather than another data source, must be clearly described. The SWHS is a unique resource, and thus, SWHS data will be used for analyses where other studies cannot provide adequate or similar information. In addition, proposals to evaluate highly speculative hypotheses are not considered appropriate and will not be approved. Finally, analyses which are either already funded or have been proposed by SWHS investigators will not be considered for approval.

3. Study proposals will be reviewed within about four weeks of proposal submission. A decision to accept, accept pending revisions, or reject a proposal will be emailed to the applicant. For either of the latter two outcomes, a summary of the reasons for the External Advisory Board decision will be provided. An “accept pending revisions” will be given if the proposal has considerable scientific merit, yet one or more issues need to be addressed before the project can proceed. Arrangements will be made to provide an expedited review of a revised proposal. For proposals that will require the development of funding outside the proposing organization, the approval process described above must be factored into the timing of any grant application. The SWHS Investigators cannot take responsibility for missed deadlines.

B. Conducting Studies Using the SWHS Resources

1. The exact nature and scope of the project must be described in a written collaborative agreement and signed by the external collaborator, the primary SWHS investigator, and a representative from each investigator’s institution. Use of data (or other covariate data) from the SWHS is limited to the defined, specific project for which the approval was obtained. If further research or analytic activities develop from the original project, the external collaborator must obtain appropriate approval for such activities by submitting a proposal amendment. In signing the collaborative agreement, external collaborators also will be confirming that they have read these guidelines (“Guidelines for use of the Shanghai Women’s Health Study data”) and both understand and agree to comply with them.

2. Since no funds have been allocated to manage the development of these outside collaborative arrangements, all costs must be borne by the external collaborating institution. Unless the initial development and review of the proposal requires substantial data exploration to determine feasibility, it is not anticipated that this cost would exceed $5,000/proposal. The actual cost will be based on the time required of an SWHS investigator and programmer to determine approximate case numbers that might be considered appropriate for the proposed analyses and related exposure distributions.

3. Outside collaborators must provide a draft of any grant proposal (e.g., NIH grant) to the collaborating SWHS investigator at least one month prior to the application due date. This will allow the SWHS investigator an opportunity to provide feedback and will provide time to obtain any additional data (e.g., other exposure distributions) that will maximize the probability of funding for the proposal. Failure to meet this deadline will result in delay of submission. The primary SWHS investigator will provide a letter of support to the external investigator to be included in the application indicating SWHS interest in collaborating on the proposed study.

4. Study Costs
(a) External collaborators must provide funds to cover the cost of initial programming needed to identify cases and exposure distributions.

(b) The cost of all pilot studies required to determine the feasibility and validity of the proposed project must be assumed by the potential external collaborator.

(c) At least one SWHS investigator should be included as a co-investigator (with appropriate time commitment) on any grant proposal where use of SWHS data is proposed. The level of effort will vary according to the size and complexity of the project, but will usually be 5% to 10% FTE per year.

(d) To ensure integrity of SWHS data, in general, no original data will be sent to outside investigators. Secondly, because of the complexity of the database and the SWHS investigators’ knowledge of the strengths and limitations of these data, substantial input is required of SWHS investigators to ensure both valid and maximal use of the available data. For these reasons, the SWHS Data Management and Statistical Core (DMSC) will perform the analyses for all outside collaborators. Analysis plans will be drawn up by the outside collaborator in conjunction with the primary SWHS investigator; these plans will be given to the DMSC statistician who will oversee all analyses. With good justifications, exceptions can be made to provide a subset of SWHS data, typically, on a few well-defined exposure variables for pooling projects, such as consortium studies.

The Applicant should have funds to cover SWHS personnel effort (and other costs) associated with preparing data sets and conducting data analyses. Upon approval of the Request, SWHS staff will provide the Applicant with an estimate of the hours and costs required to carry out the work. Routine Requests requiring less than 10 hours to fulfill, such as the preparation of limited data sets, simple tables displaying tabulations of study data, or straightforward statistical computations may be handled as a free service. If 10 or more hours are required to complete the request, the Applicant will be either requested to provide funds to support an appropriate amount of time for SWHS personnel (such as statisticians or/and programmers) or billed according to the following fee schedule:

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If desired, prior to submitting the Request, the Applicant may contact the primary SWHS investigator(s) he/she works with to estimate the anticipated effort needed to complete a Request.

(e) The arrangement for payments will be made through formal subcontracts with Vanderbilt University Medical Center, in which full overhead as approved by NIH will be considered a direct cost to the proposing institution cost base.

5. Human Subjects Considerations

(a) It is PI’s obligation to comply with the human subject protection policies and to obtain appropriate approval from institute of the leading investigator’s Human Research Protection Program prior to implementation.

(b) As analyses of genetic susceptibility to disease are associated with complex ethical considerations, a full discussion of the ethical implications of these analyses must be part of the initial proposal. Investigators should be aware that analyses that identify women at very high risk of disease are particularly problematic in this regard.

6. The programs used for analysis must be carefully reviewed and signed off on by an SWHS epidemiologist and statistician in addition to the study programmer and the external collaborating investigator. Importantly, the sign off must be by an SWHS investigator who understands how the cases and population for analysis are being defined, is familiar with SWHS variable definitions, and can understand the code generated by the programmer.
7. A proposed timeline for completion of projects should be discussed prior to submission of any grant. All projects need to be completed within the constraints of the current SWHS system. Although additional staff may be hired if they are needed consistently, it is not possible to substantially increase (and then decrease) staffing levels for any single project. SWHS facilities do not allow for such staffing changes and it is not possible to adequately train new technicians in a sufficiently short period of time to allow such changes. At the beginning of a project, external collaborators should review with the SWHS a proposed schedule for project completion and may contact the Project Director to discuss study progress.

8. The external collaborator must agree to keep the SWHS investigators updated on the progress of the study by providing either a written or verbal report at least every year. Failure to adhere to a reasonable progress schedule (as assessed by the External Advisory Board) could lead to termination of the collaborative relationship with no further data tables or additional analyses provided.

C. Data Analysis and Publication Issues

1. The external collaborating investigator should forward all analysis results to the SWHS. All primary data sets of laboratory results will be maintained in the SWHS database.

2. All data analyses will be conducted at Vanderbilt by DMSC of the SWHS (see section B.4.d above). The most efficient way for these analyses to be accomplished will be for the outside investigator and the collaborating SWHS investigator to agree on the analysis plan in advance (to whatever extent possible). The external collaborating investigator will provide to the statistician a set of data analysis requests and an outline template of result tables that indicates how the results are to be presented. The DMSC of the SWHS will proceed to complete the analyses and return the completed tables to the collaborating investigator. In completing the analysis plan, the SWHS investigator also will work as needed with the statistician in supervising the SWHS programmer assigned to the project.

3. At least one member of the SWHS investigative team should be a coauthor on any manuscript resulting from this collaboration and, as such, will need to sign-off on any manuscript prior to its submission for publication. This will take the form of a brief note indicating review and approval of the final manuscript by the SWHS investigator. External investigators should plan on the entire process taking at least 4 weeks (and longer if there are issues to be resolved concerning analysis or interpretation of the data). Any initial presentation of these data at meetings also must receive sign-off from the designated SWHS investigator(s).

4. Any dispute regarding data interpretation may be brought to the External Advisory Board for consideration. Where appropriate, the External Advisory Board will seek additional consultation from independent experts. Since the External Advisory Board meets as a group only once per year, considerable delay in coming to a resolution could occur. Therefore, it behooves all collaborating investigators to work closely with the designated SWHS investigator in resolving any dispute. Final decisions rest with Dr. Zheng, the SWHS Principal Investigator, in consultation with the External Advisory Board.
Guidelines for Use of Biological Samples Collected in the Shanghai Women’s Health Study

A. Submitting a Proposal

1. Any investigator wishing to develop a collaboration with the Shanghai Women’s Health Study (SWHS) to use SWHS biospecimens should submit a detailed research proposal. The format of the proposal is described in detail below.

2. The proposal’s format is similar to an NIH grant (i.e., specific aims, background and significance, preliminary studies, and methods) but should be no longer than 6 pages in length. The proposal should also include required variables, biospecimen type and amount, assay methods, laboratory name, justification for using the SWHS resources and timeline. The reasons for proposing use of the SWHS biospecimens, rather than another source, must be clearly described. Although the SWHS biorepository is a unique resource, it is also finite. Therefore, SWHS biospecimens will be used only for analyses where other, less precious, biospecimens cannot provide adequate or similar information. The assessment of markers of disease prognosis will generally not be considered an appropriate use of the SWHS biorepository. In addition, proposals to evaluate highly speculative hypotheses are not considered appropriate and will not be approved. Finally, laboratory analyses which are either already funded or have been proposed by SWHS investigators will not be considered for approval.

3. Study proposals will be reviewed three times per year. Submission deadlines are February 1, June 1, and October 1. Before an approval is granted, the following issues must be addressed to confirm that a particular association can be reasonably evaluated using SWHS biorepository samples.

   (a) Appropriateness of using blood samples collected in EDTA and urine samples spiked with vitamin C. SWHS blood samples were collected using EDTA as the anticoagulant, and urine samples were spiked with vitamin C. The laboratory needs to confirm that these tubes are routinely accepted for the analysis of interest; otherwise, a pilot study will need to be conducted to establish that sodium heparin will not interfere with assay performance.

   (b) Laboratory assay to be used. All assays must be conducted using the best available technology to ensure that the appropriate parameter is assayed, the volume of sample required is minimized, and the assay reproducibility is maximized. The definition of “acceptable” sample volume will be determined on a study-by-study basis and will depend in large part on the importance/priority of the study hypothesis. In the proposal, the applicant should be clear in describing the various assay methods currently available and their rationale for using the specific assay being proposed.

   (c) Reproducibility of the laboratory assay. The laboratory conducting the analyses must be able to conduct the assay with a high degree of precision (i.e., low coefficient of variation or high reliability coefficient). This information must be obtained through a blinded evaluation of the laboratory. Unfortunately, coefficients of variation provided by laboratory investigators are not sufficient, as, in our experience, these data do not always reflect the true magnitude of laboratory error. The evaluation must be recent and, if at all possible, should have been performed by the same technician who will be conducting the study analyses.

   (d) Range of the biomarker in the SWHS cohort. For many biomarkers of interest, knowledge of a usual range in an adult population will be sufficient (e.g., plasma antioxidant levels); in this instance, the usual range and how this range was determined (i.e., in what population) should be briefly described. However, for other assays, where the range may vary substantially by population (e.g., plasma levels of DDE/PCBs), a population-specific distribution of biomarker levels should be provided. If necessary, a pilot study to determine levels observed in the SWHS may need to be conducted prior to receiving final approval for conducting a project.

   (f) Stability of the biomarker over time (i.e., how well a single measure reflects long-term blood levels). In the SWHS cohort overall, only one blood and urine sample per participant was collected. Thus, data must be available to indicate that a single measurement provides a sufficiently integrated measure of longer term
exposure (generally the exposure of interest with chronic diseases) that an association between the biomarker and disease could reasonably be detected, if it indeed exists. If these data are not already available, applicants should consider conducting a pilot study to assess stability over a minimum of a 6-month period.

4. It is anticipated that the decision to accept, accept pending revisions, or reject a proposal will be made within about four weeks of proposal submission. For either of the latter two outcomes, a summary of the reasons for the decision will be provided. An “accept pending revisions” will be given if the proposal has considerable scientific merit, yet one or more issues need to be addressed before the project can proceed. Arrangements will be made to provide an expedited review of a revised proposal. For proposals that will require the development of funding outside the proposing organization, the approval process described above must be factored into the timing of any grant application. The SWHS investigators cannot take responsibility for missed deadlines.

B. Conducting Studies Using the SWHS Biorepository

1. The exact nature and scope of the project must be described in a written collaborative agreement and signed by the external collaborator, the primary SWHS investigator, and a representative from each investigator’s institution. Use of biomarker data (or other covariate data) from the SWHS is limited to the defined, specific project for which the External Advisory Board approval was obtained. If further research or analytic activities develop from the original project, the external collaborator must obtain appropriate approval for such activities. In signing the collaborative agreement, external collaborators also will be confirming that they have read these guidelines (“Guidelines for Use of Biological Samples”) and both understand and agree to comply with them.

2. Since no funds have been allocated to manage the development of these outside collaborative arrangements, all costs must be borne by the collaborating outside investigator’s institution. Unless the initial development and review of the proposal requires substantial data exploration to determine feasibility, it is not anticipated that this cost would exceed $5,000/proposal. The actual cost will be based on the time required of an SWHS investigator and programmer to determine approximate case and control numbers that might be considered appropriate for the proposed analyses and related exposure distributions.

3. Outside collaborators must provide a draft of any grant proposal (e.g., NIH grant) to the collaborating SWHS investigator at least one month prior to the application due date. This will allow the SWHS investigator an opportunity to provide feedback, and will provide time to obtain any additional data (e.g., other exposure distributions) that will maximize the probability of funding for the proposal. Failure to meet this deadline will result in delay of submission. This institutional policy also is followed by all SWHS investigators and cannot be circumvented. The primary SWHS investigator will provide a letter of support to the external investigator to be included in the application indicating SWHS interest in collaborating on the proposed study.

4. Every effort will be made to preserve biological samples collected in the SWHS so that these precious samples can be used for future studies. Multiplex assay technologies will be used when appropriate to preserve samples.

5. Study Costs

(a) External collaborators must provide funds to cover the cost of retrieving, aliquoting and shipping of specimens, receiving and cataloguing of returned specimens, data entry of results and for additional freezer space (necessitated by the aliquoting of samples). Funds also must be provided for the initial programming needed to identify case and control samples, prepare data sets, and perform statistical analyses (if appropriate) (see fee schedules in 4(e) below).

(b) In addition to the cost of the laboratory analysis of case-control samples, funds must be available to conduct (a) a test of laboratory reproducibility immediately prior to submitting any study samples if the previous assessment occurred 6 or more months in the past and (b) for quality control specimens to be analyzed along with the study samples (in approximately a 1:10 ratio).
(c) The cost of all pilot studies required to determine the feasibility and validity of the proposed project may be assumed by the potential external collaborator.

(d) At least one SWHS investigator should be included as a co-investigator (with appropriate time commitment) on any grant proposal where use of SWHS biosamples is proposed. The level of effort will vary according to the size and complexity of the project but will usually range from 5% to 10% FTE per year.

(e) To ensure integrity of SWHS data, it is the general policy of the SWHS that no data leave Vanderbilt University Medical Center. Secondly, because of the complexity of the database and the SWHS investigators’ knowledge of the strengths and limitations of these data, substantial input is required of SWHS investigators to ensure both valid and maximal use of the available data. For these reasons, all data analyses will be carried out by the Data Management and Statistical Core (DMSC) of the SWHS. The outside collaborator in conjunction with the primary SWHS investigator will draw up analysis plans; these plans will be given to the DMSC statistician who will oversee all analyses. With good justifications, exceptions can be made to provide a subset of SWHS data, typically, on a few well-defined exposure variables for pooling projects, such as consortium studies.

The Applicant should have funds to cover SWHS personnel effort (and other costs) associated with preparing data sets and biological samples as well as conducting data analyses. Upon approval of the Request, SWHS staff will provide the Applicant with an estimate of the hours and costs required to carry out the work. Routine Requests requiring less than 10 hours to fulfill, such as the preparation of limited data sets, simple tables displaying tabulations of study data, or straightforward statistical computations may be handled as a free service. If 10 or more hours are required to complete the request, the Applicant will be either requested to provide funds to support an appropriate amount of time for SWHS personnel (such as statisticians, programmers, and/or lab personnel) or billed according to the following fee schedule:

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If desired, prior to submitting the Request, the Applicant may contact the primary SWHS investigator(s) he/she works with to estimate the anticipated effort needed to complete a Request.

(f) The arrangement for payments will be made through formal subcontracts with Vanderbilt University Medical Center in which full overhead as approved by NIH will be considered a direct cost to the proposing institution cost base.

6. Human Subject Considerations

(a) It is PI’s obligation to comply with the human subject protection policies and to obtain appropriate approval from the leading investigator institute’s Human Research Protection Program prior to implementation.

(b) As analyses of genetic susceptibility to disease are associated with complex ethical considerations, a full discussion of the ethical implications of these analyses must be part of the initial proposal. Investigators should be aware that analyses that identify women at very high risk of disease are particularly problematic in this regard.

7. Before any aliquoting of samples is begun, the programs used to generate cases and controls must be carefully reviewed and signed off on by an SWHS epidemiologist and DMSC statistician in addition to the study programmer and the external collaborating investigator. Importantly, the sign-off must be by an SWHS investigator who understands how the cases and controls are being defined, is familiar with SWHS variable definitions, and can understand the code generated by the programmer. Laboratory assay of the wrong cases or controls, because of errors in their initial identification, can be very expensive and would waste a precious resource.
8. To the extent possible, all analyses will be conducted as a single batch with appropriate masked QC samples added to the batch. If, as is frequently the case, a large number of samples are being assayed in a study, the precision of the assay must be monitored on an ongoing basis using masked QC samples. Results from these QC samples must be reported on a batch-by-batch basis to the SWHS investigator who will be responsible for monitoring reproducibility.

9. A proposed timeline for completion of aliquoting projects should be discussed prior to submission of any grant. All projects need to be completed within the constraints of the current SWHS system. Although additional staff may be hired if they are needed consistently, it is not possible to substantially increase (and then decrease) staffing levels for any single project. SWHS facilities do not allow for such staffing changes and it is not possible to adequately train new technicians in a sufficiently short period of time to allow such changes. At the beginning of a project, external collaborators should review with the SWHS a proposed schedule for project completion and may contact the director of the SWHS Biorepository Core to discuss study progress.

10. The external collaborator must agree to keep the SWHS investigators updated on the progress of the study by providing either a written or verbal report at least annually. Failure to adhere to a reasonable progress schedule (as assessed by the External Advisory Board) could lead to termination of the collaborative relationship with no further data tables or additional analyses provided.

11. Any biological sample remaining after the completion of the approved laboratory assays must be returned promptly to the SWHS sample archive.

C. Data Analysis and Publication Issues

1. The external collaborating investigator should forward all laboratory results to the SWHS. All primary data sets of laboratory results will be maintained in the SWHS database.

2. All data analyses will be conducted at Vanderbilt by DMSC of the SWHS (see section B.5.e above). The most efficient way for these analyses to be accomplished will be for the outside investigator and the collaborating SWHS investigator to agree on the analysis plan in advance (to whatever extent possible). Once the laboratory assays are complete and results sent to the SWHS, the external collaborating investigator will provide to the DMSC statistician a set of data analysis requests and template of result tables that indicates how the results are to be presented. The SWHS DMSC will proceed to complete the analyses and return the completed tables to the collaborating investigator. In completing the analysis plan, the SWHS investigator also will work as needed with the DMSC statistician in supervising the SWHS programmer assigned to the project.

3. At least one member of the SWHS investigative team should be a coauthor on any manuscript resulting from this collaboration and, as such, will need to sign off on any manuscript prior to its submission for publication. External investigators should plan on the entire process taking at least 4 weeks (and longer if there are issues to be resolved concerning analysis or interpretation of the data). Any initial presentation of these data at meetings also must receive sign-off from the designated SWHS collaborating investigator(s).

4. Any dispute regarding data interpretation may be brought to the External Advisory Board for consideration. Where appropriate, the External Advisory Board will seek additional consultation from independent experts. Since the External Advisory Board meets as a group only once per year, considerable delay in coming to a resolution could occur. Therefore, it behooves all collaborating investigators to work closely with the designated SWHS investigator in resolving any dispute. Final decisions rest with Dr. Zheng, the SWHS Principal Investigator, in consultant with the External Advisory Board.