

**Guidelines for External Collaborators:
Use of the Adventist Health Study-2 Archived Data**

A. Submitting a Proposal

A.1. Letter of intent: Investigators wishing to develop a collaboration with the Adventist Health Study-2 (AHS-2) group to use the data archive are asked to initially e-mail a “letter of intent” to Dr. Gary Fraser, AHS-2 Director (gfraser@llu.edu) and/or Dr. Michael Orlich, Co-Director (morlich@llu.edu). The letter of intent should briefly describe the nature of the proposed hypothesis. A letter of intent may be submitted at any time throughout the year. It will be reviewed by Dr. Fraser and/or Dr. Orlich and the AHS-2 team of investigators at a regular monthly Coordinators’ Committee meeting. If a project is judged feasible (given database resources), of substantial scientific interest, is not currently being pursued by another investigator, and is not currently under consideration (typically listed as a specific aim of a submitted or funded grant), the proposed investigation outlined in the letter of intent will be approved. It is also possible that the applicant will be asked to submit additional information, if it is unclear from the letter whether the research fulfills the requirements. The applicant will be notified of the decision within approximately 30 days after the letter of intent was submitted.

A.2. Study proposal: If the proposed investigation outlined in the letter of intent is approved, the applicant is asked to submit a 3-5 page proposal to the AHS-2 Proposal Review Committee (submit through Dr. Fraser or Dr. Orlich). Submission deadlines are March 15, July 15, and November 15. The proposal should include the following:

- Rationale
- Hypothesis being proposed
- Scientific significance of the project
- Cohort participant data variables required for analysis
- Assurance of power
- Anticipated weaknesses/challenges
- Reasons for proposing use of AHS-2 data, rather than another source
- Curriculum vitae

It is anticipated that the Proposal Review Committee’s decision will be made within four to eight weeks of proposal submission. The Review Committee will decide to accept, accept pending revisions, or reject a proposal. 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, which addresses the concerns of the Review Committee.

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 Review Committee and AHS-2 investigators cannot take responsibility for missed deadlines.

A.3. Data sets available: AHS-2 data from the following sources may be available for approved collaborative research projects. More detailed descriptions of the available data variables will be provided upon approval of the letter of intent for help in crafting the project proposal.

- Baseline questionnaire data
- Calibration study data
- Biomarkers
- Outcome data (cancer incidence, mortality)

B. Conducting Studies Using the AHS-2 Data Archive

B.1. Collaborative agreement: If the proposal is approved, a primary AHS-2 investigator will be identified to work with the external collaborator to facilitate the research. The exact nature and scope of the project must be described in a written collaborative agreement and signed by the external collaborator and the primary AHS-2 investigator. Use of data from the AHS-2 cohort is limited to the defined, specific project for which 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 agreement, external collaborators also will be confirming that they have read the guidelines outlined in this document and both understand and agree to comply with them.

B.2. Preliminary data: An AHS-2 investigator and programmer will provide approximate case numbers, exposure distributions, and other related data that may be used for preparing a grant application. All costs for this effort must be borne by the collaborating outside investigator's institution based on the time required to produce the data. No charge will be made for minimal effort.

B.3. Grant funding: Outside collaborators must provide a draft of any grant proposal (e.g. NIH grant) to the collaborating AHS-2 investigator at least 6 weeks prior to the application due date. This will allow the AHS-2 investigator an opportunity to provide feedback, and will provide time to obtain any additional data, as noted above, that will maximize the probability of funding for the proposal.

In keeping with the policies of Loma Linda University and the Adventist Health Study-2, the final grant proposal must be reviewed by Drs. Gary Fraser or Michael Orlich in the Adventist Health Study-2 and by the Associate Vice President for Research Affairs or his designee in Loma Linda University Research Affairs, at least 2 weeks before submission. Failure to meet this deadline will result in delay of submission. This institutional policy also is followed by all AHS-2 investigators and cannot be circumvented. The primary AHS-2 investigator will provide a letter of support to the external investigator to be included in the application indicating the Adventist Health Study-2 group's interest in collaborating on the proposed study.

B.4. Study costs

(a) As noted above (section B.2), external collaborators must provide funds to cover the cost of initial programming by AHS-2 staff, needed to identify cases, exposure distributions or other related data if necessary.

(b) Should substantial pilot research be needed, the cost of all pilot studies required to determine the feasibility and validity of the proposed project must be assumed by the external collaborator.

(c) Because of the complexity of the database and the AHS-2 investigators' knowledge of the strengths as well as the limitations of these data, substantial input is required from AHS-2 investigators to insure both valid and maximal use of the available data. Therefore, at least one AHS-2 investigator must be included as a co-investigator on any grant proposal where use of AHS-2 data is proposed. Any non-academic outside user (e.g. from a private company) similarly must be able to provide salary support for an investigator. The level of effort will vary according to the size and complexity of the project but will be expected to range from 5% to 10% FTE per year. For more complex investigations, funding for an AHS-2 statistician may also be required.

(d) To insure integrity of the AHS-2 data and comply with privacy commitments for our study participants, it is the policy of the AHS-2 that no data are copied from the Adventist Health Study-2 computer. Therefore, all analyses must be conducted on our computer system. It is possible for all programming to be done by the external collaborator or a designated person at the collaborating institution. The programmer would need to learn our computer system, data files, and analysis methods, which may require a visit to the Adventist Health Study-2 for an introductory session. A Data Use Agreement will be signed and proof of Human Subjects certification (such as completion of the CITI course) must be submitted. The programmer will be issued a logon to the Adventist Health Study-2 computer for remote access. Even if outside collaborators do their own programming, some input from the Adventist Health Study-2 programmers is needed, and those costs must be covered by the outside collaborator. Alternatively, depending on the availability, the external collaborator may pay for the cost of having an AHS-2 programmer do all analyses. The cost is dependent upon the complexity of the investigation but is typically about 20% FTE.

(e) The arrangement for payments will be through formal subcontracts with Loma Linda University School of Public Health, including full overhead.

B.5. Human subjects considerations: All projects must receive approval from the Loma Linda University Institutional Review Board prior to implementation. The preparation of the IRB application is primarily the responsibility of the external collaborators, in coordination with the primary collaborating AHS-2 investigator. Where the Proposals Review Committee determines that the proposed data use is in harmony with the original AHS-2 purpose and informed consent, the IRB application will be accomplished by filing a Change Request Form. Also, all investigators who have access to AHS-2 data on the computer must complete a Human Subjects certification, such as the CITI course. External collaborators are also responsible for any IRB review or approval required by their home institution.

B.6. Study timeline: A proposed timeline for completion of projects should be discussed prior to submission of any grant (e.g. an NIH grant proposal). All projects need to be completed within the constraints of the current AHS-2 staffing levels. It is not possible to substantially increase (and then decrease) staffing levels for any single project. At the beginning of a project, external collaborators should review with the AHS-2 a proposed schedule for project completion. Discussions of project timeline and progress will be primarily with the primary AHS-2 investigator involved in the collaboration, but will require review by Drs. Fraser or Orlich.

B.7. Progress reports: The external collaborator must agree to keep the AHS-2 investigators updated on the progress of the study by providing a written progress report at least yearly. Failure to adhere to a

reasonable progress schedule (as assessed by the Proposals Review Committee) could lead to termination of the collaborative relationship with no further data tables or additional analyses provided.

C. Data Analysis and Publication Issues.

C.1. Use of AHS-2 computing resources: As noted above (section B.4.d), all primary data, computer programs, and analysis results must be maintained on the AHS-2 server, and all data analyses will be conducted on this or other linked in-house computers. SAS or R are typically the computer languages used for data analyses. If an external collaborator needs to use a different programming language, this must be discussed with the AHS-2 investigator before analyses begin.

C.2. Analysis plan and procedure: The most efficient way for analyses to be accomplished will be for the external investigator and the collaborating AHS-2 investigator to agree on an analysis plan, including variables and covariates to be used, in advance (to whatever extent possible). If analyses are being conducted by an AHS-2 programmer, the external collaborating investigator will provide a set of data analysis requests and a series of empty tables that indicate how the results are to be presented. In completing the analysis plan, the AHS-2 investigator will work as needed in supervising the AHS-2 programmer assigned to the project. The external collaborating investigator should forward all analysis results to the AHS-2 investigator for review and discussion.

C.3. Presentation of results: When data tables of results are finalized, these tables and a written abstract will be presented by the AHS-2 investigator at a regular AHS-2 study meeting. This provides an opportunity for other investigators to comment and make suggestions for improvement. Based on the comments, additional analyses may be required. Presentation of results at an AHS-2 study meeting is required for all research that uses AHS-2 data prior to submission for publication.

C.4. Review of computer program code: It is required that the code used for analysis must be carefully reviewed by an AHS-2 epidemiologist in addition to the study programmer/statistician and the external collaborating investigator. Importantly, the sign off must be by an AHS-2 investigator who understands how the cases and population for analysis are being defined, is familiar with AHS-2 variable definitions, and can understand the code generated by the programmer. This computer code review is required for all investigations that use AHS-2 data.

C.5. Authorship and manuscript review: At least one member of the AHS-2 investigative team will 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. All manuscripts must also be submitted for review to Drs. Fraser or Orlich, and approval must be obtained before a manuscript can be submitted to a journal for publication. This additional review is also required of all AHS-2 investigators.

C.6. Manuscript disputes: Any dispute regarding data interpretation may be brought to the full AHS-2 Coordinators' Committee for consideration. Where appropriate, this Committee will seek additional consultation from independent experts. This committee may only be able to review such matters every 3-6 months, and so considerable delay in coming to a resolution could occur. Therefore, it behooves all collaborating investigators to work closely with the designated AHS-2 investigator in resolving any dispute. Final decisions rest with Drs. Fraser and Orlich.