Guidelines for External Collaborators:

Use of the Adventist Health Study-2 Biospecimens

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 biospecimens (e.g. plasma) are asked to initially email a "letter of intent" to Dr. Gary Fraser (gfraser@llu.edu) , AHS-2 Director, and/or Dr. Michael Orlich (morlich@llu.edu), Co-Director. The letter of intent should briefly describe the nature of the proposed biospecimens to be used and the hypotheses related to their use.

AHS-2 biospecimens are a unique and finite resource, therefore access will only be granted for investigations where other biologic samples cannot provide adequate or similar information. Of note, the assessment of markers of disease prognosis will generally not be considered an appropriate use of the AHS-2 archive. Similarly, proposals to evaluate highly speculative hypotheses are not considered appropriate. Investigators should also be aware that analyses which identify subjects at very high risk of disease are particularly problematic and may require additional approval for ethics consideration.

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 the biospecimen and data 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 letter of intent for collaboration 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 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 will be asked to provide a more detailed description of the study to be performed with AHS-2 biospecimens. In a document of no more than 10 pages, the applicant should provide the information demonstrating the biospecimens are "fit for purpose" for the biomarker or other analyses proposed. Proposals should be submitted to Dr. Gary Fraser (gfraser@llu.edu) and/or Dr. Michael Orlich (morlich@llu.edu), and will be reviewed at the next available meeting of the Biorepository Advisory Group, which includes the PI of the AHS-2. 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
- Proposed biospecimens (and quantities) to be used
- Proposed uses of the biospecimens (assays)
- Reasons for proposing use of the AHS-2 biological samples, rather than another source
- Discussion for foreseeable ethical implications of the analyses proposed
- Any cohort participant data variables required for analysis

- Assurance of statistical power
- Anticipated weaknesses/challenges
- Curriculum vitae

It is anticipated that the Biorepository Advisory Group's decision will be made within twelve weeks of proposal submission. The Biorepository Advisory Group will decide to accept, accept pending revision, 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 of 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 Biorepository Advisory Group.

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 Advisory Committee and AJHS-2 investigators cannot take responsibility for missed deadlines.

A.3. Biospecimens available: AHS-2 biospecimens of the following types (generally ≤ 2500) may be available for approved collaborative research projects. More detailed descriptions and updated quantities of the available biospecimens will be provided upon inquiry for help in crafting the project proposal. *Available types:* serum, plasma, packed erythrocytes, buffy coat, urine.

B. Conducting Studies Using the AHS-2 Biospecimens

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 specimens (and 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. Since no funds have been allocated to manage the development of these outside collaborative arrangements, 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 six 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 preliminary programming by AHS-2 staff needed to identify cases, exposure distributions or other related data if necessary.

(b) External collaborators must provide funds to cover the cost of retrieving, aliquoting, and shipping of specimens from the AHS-2 Biorepository. An estimate of study-related bio-repository charges will be provided for inclusion into grant requests. Funds also must be provided for the initial programming needed to identify case and control samples.

(c) In addition to the cost of the laboratory analysis of case-control samples, funds must be available for quality control specimens to be analyzed along with the study samples (in approximately a 1:10 ratio).

(d) 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.

(e) 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 also may be required.

(f) 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 AHS-2 computer system. 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 the LLU computer system, data files, and analysis methods, which may require a visit to Loma Linda University for an introductory session. A Data Use Agreement would be signed and proof of Human Subjects certification (such as completion of the CITI course) must be submitted. The programmer would be issued a logon to the AHS-2 computer for remote access. Inevitably, even if outside collaborators do their own programming, some input from AHS-2 programmers is needed, and those costs would have to be covered by the outside collaborator. Alternatively, the external collaborator may pay for the cost of having an AHS-2 programmer do all analyses, if one is available. The cost is dependent upon the complexity of the investigation but is typically about 20% FTE.

(g) The arrangement for payments will be through formal subcontracts with Loma Linda University, 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. Case/control selection: Before any aliquoting of specimens is begun, the case control selection specifications and resulting selected subjects must be carefully reviewed and signed off on by an AHS-2 epidemiologist in addition to the study programmer and the external collaborating investigator. Importantly, the sign off must be by an AHS-2 investigator who understands how the cases and controls are being defined and is familiar with AHS-2 variable definitions.

B.7. Laboratory analyses and results: 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 biorepository staff who will work with the AHS-2 and external investigators to monitor reproducibility.

Any plasma, DNA, or RBC sample remaining after the completion of the approved laboratory assays must be returned promptly to the AHS-2 sample archive.

The external collaborating investigator should forward all laboratory results to AHS-2. All primary data sets of laboratory results will be maintained on the AHS computer.

B.8. 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.9. 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 computer: 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 programs: 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.