

4.0 ANCILLARY STUDIES POLICY

4.1 General Policy

To enhance the value of ARIC, the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies and to promote the advancement of science. Nevertheless, to protect the integrity of ARIC and the privacy of its participants, such ancillary studies must be reviewed and approved by the Steering Committee, and by NHLBI through its ARIC Observational Study Monitoring Board (OSMB), before their inception. In general, ancillary studies require outside (non-ARIC) funding. All ancillary studies must send to the ARIC coordinating center a yearly update on status.

4.2 Definition of Ancillary Study

An ancillary study is one based on information from ARIC participants in an investigation that is not described in the ARIC protocol and involves data collection or data analyses under additional funding that are not included as part of the routine ARIC data set or data analyses. The core ARIC study includes the use of blood and DNA stored for case-control studies approved by the Steering Committee; these are not considered ancillary studies. In general, ancillary studies require external (non-ARIC) funding. Funding must cover the cost incurred by the ARIC Laboratories (e.g., to process or ship samples), and to the Coordinating Center (for tasks such as sample selection, preparing and documenting analysis files, participating in statistical analysis, and integrating the new ancillary data back into the combined ARIC database). No funds for this purpose are available within the Study. A request for DNA samples to replicate a non-ARIC study's results is also considered to be an ancillary study.

4.3 Requirements for Approval of an Ancillary Study

An ancillary study must receive approval before a grant to support it is submitted. Approval will be based on finding that the ancillary study will have scientific merit but will not do any of the following:

- a. Interfere with the completion of the main objective of ARIC.
- b. Adversely affect participant cooperation in compliance in ARIC.
- c. Create a serious diversion of study resources (personnel, equipment or study samples), either locally or centrally.
- d. Jeopardize the public image of ARIC.
- e. Use ARIC study contract resources without reimbursement.

At least one ARIC investigator (paid off an ARIC contract or subcontract) must be included as a co-investigator in each proposal. This investigator, collaborating with the ancillary study PI, will facilitate preparation of the ancillary study proposal, its submission to the ARIC Steering Committee and NHLBI, and subsequent communications between the collaborating studies. ARIC investigators other than those submitting the proposal may request to become collaborators on a proposal if they have a specific interest in the topic.

4.3.1 Preparation of Request for Approval of an Ancillary Study

Scientific questions about preparing an ancillary study that are not addressed below can be sent to ARIC-AS@unc.edu at the coordinating center.

To apply for approval of an ancillary study, a written request on the ARIC Ancillary Study Proposal Form (<https://sites.csc.unc.edu/aric/ancillary-studies-pfg/>) should be submitted to ARIC-AS@unc.edu. The Ancillary Study Proposal form is in Appendix A.

4.3.2 Review of Ancillary Study Proposals

The Steering Committee will review and will approve, reject or request modification of ancillary study proposals in a timely manner (generally 3-6 weeks). The ARIC Laboratory Committee will be asked to first approve ancillary studies using stored biological samples to ensure appropriate use (see separate document on ARIC Sample Distribution Policy). Approval by NHLBI, following review and recommendations of the ARIC OSMB is also required. Exceptions to the need for OSMB approval may be granted by the OSMB Executive Secretary in case of studies with no participant risk or burden. Proposals for funding any ancillary study can be submitted only after ARIC Steering Committee approval is granted.

The key criteria for approval of proposals are scientific merit, potential for enhancing ARIC's goals, and impact on the main ARIC study's resources and participants. In addition, the plan for reimbursing all ancillary study costs must be adequate. A review form specifying the criteria considered in review of ancillary studies is in Appendix B.

4.3.3 Amendments of Ancillary Study Proposals

Amendments to ancillary study proposals (e.g., adding analytes to be measured) require approval via submission of a revised proposal with a note describing the changes.

4.3.3 Yearly Status on Progress of Ancillary Study

A progress report on the status of the ancillary study is required to be reported to the Coordinating Center each year before November 1 so that the Policy Board can receive an update on the progress. The report is made on the Update on ARIC Ancillary Study Yearly Report Form (Appendix C).

4.4 Analysis and Publication of Results of Ancillary Studies

The principles of this policy are to provide participant protection (ensure use of data does not exceed informed consent), coordination of efforts to avoid duplication of work, and to minimize barriers to publication of Ancillary Studies.

The investigator of the ancillary study, and if necessary the Steering Committee, will consult with the Coordinating Center during data analysis to ensure that all study data used in analysis of ancillary results are consistent with data in the main study database. Manuscripts and abstracts proposed for analysis must be approved in advance by the ARIC Steering Committee. This

procedure is necessary to establish authorship and prevent overlap in the publication effort. Approval for manuscripts and abstracts is sought by submitting the proposal on a standard form to the Coordinating Center. Completed manuscripts and abstracts resulting from ancillary studies shall also be submitted for review and require approval by the Steering Committee prior to submission for publication or presentation. The investigator who assumes lead responsibility for the ancillary study shall generally be listed as an author. The phrase “ARIC Study” should be included in the title and listed as a key word whenever possible.

An exception to this policy may be made for large ancillary studies that have their own coordinating centers and publication committees. The exception to the policy would apply to manuscript proposals relying primarily on data unique to the ancillary study (i.e., not available in the ARIC core study). To date, only Sleep Heart Health Study, the Jackson Heart Study, and Family Heart Study, and some other consortia qualify for this exemption. However, even these studies should submit a copy of their manuscript proposal to the ARIC publications committee. These proposals do not routinely require ARIC approval.

4.5 Feedback of Results of Ancillary Studies to Participants

Results of ancillary studies shall be reported to participants and/or their physicians if such reporting is medically useful and approved by the relevant IRB and ARIC. Once approved, such reporting should follow standard ARIC protocol for notification of participants and be coordinated via the ARIC coordinating center.

4.6 Handling of ARIC Data and Specimens

At the time of distributing ARIC specimens and/or information, the ARIC Collaborating Investigator, with help from the Coordinating Center, makes explicit arrangements with the ancillary study PI for:

- a. security of these study materials,
- b. completed Third Party Agreement if a third party or industry is supporting the study, (*Please note that the third party agreement needs to be submitted to NHLBI before the Data/Materials Distribution Agreement is completed.*)
- c. completion of our ARIC “Data and Materials Distribution Agreement” (<https://sites.csc.unc.edu/aric/ancillary-studies-pfg>)
- d. documentation of IRB approval (see documentation below), and
- e. final disposition of study materials at the conclusion of the ancillary study.

4.7 IRB Documentation

The ancillary study PI is responsible for obtaining IRB approval for the proposed study. There are two possible approaches: the single IRB (sIRB) or the local IRB. (Beginning spring 2022, the ARIC study IRB approval is maintained by Johns Hopkins as a sIRB). The ancillary study PI will indicate on the ancillary study proposal which IRB will have jurisdiction over the proposed study (sIRB through a modification of an ARIC JHU-SOM protocol (surveillance/repository or visits, another sIRB or a local IRB) based on the criteria below.

The sIRB approval is needed for all non-exempt multi-center human subjects research. Our operational definition includes the following scenarios:

- a. new data collection at more than one center either directly with ARIC participants or using medical records
- b. lab analysis of ARIC stored samples that use identifiers or require reporting data back to participants
- c. more than one center will see PHI for the study
- d. there eventually may be an FDA application.

Please refer to this link regarding sIRB: <https://grants.nih.gov/faqs#/hs-single-IRB-policy-for-multi-site-research.htm?anchor=question54849>

The Local IRB can have jurisdiction for most other applications including:

- a. proposals that only use existing ARIC deidentified data (e.g., most student projects, career development projects) will qualify as exempt or non-human subjects research
- b. exclusively single center proposals (this can include some investigators at other sites who are only coauthors or provide services but never see participants or PHI)
- c. lab studies where the ARIC component is already approved in the sIRB parent protocol. The parent sIRB ARIC protocol covers provision of specimen (by ARIC labs at Baylor, Houston and Minnesota) identified only by barcodes (which can include the ARIC ID) for approved uses (documented through an approved ancillary study with goals consistent with the consent and sIRB aims and covered by a DMDA). The provision of specimen and de-identified data (linkable by ID but without identifiers or hospitalization dates) is already covered by the ARIC sIRB. Likewise, the receipt of data and its integration into the parent ARIC data repository and sharing following NIH policies is also covered by the sIRB. **The ancillary study must provide IRB coverage for the work done once the specimen are received. The work can be multi-centered and stay under local IRBs as long as it is exempt or non-human subjects research.**

Data collected by the Ancillary Study, with thorough documentation (an archival copy of newly collected data with labels, and/or laboratory results as well as documentation on methods, visits and units used with specific instructions for using the data in analyses such as exclusions that were applied) is to be sent to the ARIC Coordinating Center one year after the conclusion of the data cleaning and closure or one year after acceptance of the primary publication, whichever comes first. After that has been done and with appropriate funding for costs, the Ancillary Study investigators will receive the integrated file containing data from the main study. This should allow sufficient time for publication of the main (ancillary) study hypothesis. This transfer is the responsibility of the ancillary study ARIC collaborator(s). The data from the ancillary study will be included in the ARIC Limited Access Data (LAD) set for distribution to outside researchers according to the established NHLBI procedures for distribution <https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-policy-for-data->

[sharing-from-clinical-trials-and-epidemiological-studies](#). LAD refers to trial or study data (both NIH and non-NIH funded), with certain deletions and recoding, that are released to requesting institutions and investigators for specific purposes and with certain restrictions and conditions.

The safety and confidentiality of the ARIC data at the collaborating institution is the responsibility of the ancillary study PI, as is the appropriate disposition of these materials after the study has been completed. Leftover DNA and laboratory specimens are destroyed or returned, as appropriate; files of ARIC data are returned or deleted, as established at the outset of the collaboration.

The Steering Committee monitors the development of the ancillary studies, receipt of funding, initiation dates, and progress. A written progress report on ancillary studies is to be made annually to the Steering Committee and the Monitoring Board. This annual report, which is solicited via the coordinating center, should include a list of data collected and/or analytes measured. For convenience, a shell document for these reports is provided on the ARIC study website (under Ancillary Studies).

Ancillary Study Principal Investigator will send completed Distribution Agreement(s) via email to ARIC-AS@unc.edu to the ARIC Coordinating Center. The Coordinating Center will review agreement(s), execute signature on behalf of ARIC and forward the agreement to the National Institutes of Health. An electronic copy with all required signatures will be retained by the Coordinating Center and sent to the Ancillary Study Principal Investigator.

4.8 Ancillary Studies Using DNA or Other Stored Samples

The ARIC project represents a unique public resource to be used by the clinical, public health and scientific community to better understand the etiology and epidemiology of atherosclerosis, its risk factors and clinical sequelae. The ARIC investigators are committed to managing the stored biologic material for the good of this endeavor. Part of this resource includes stored blood and DNA and informed consent for genetic studies of atherosclerosis on most ARIC participants.

4.8.1 Sample availability

A list of samples originally collected by ARIC is shown below and in the ARIC sample distribution policy document. Many of these aliquots have been used and may not be available for ancillary studies. In general, samples tend to have been exhausted from visits 1 and 2 on participants with arterial events and certain conditions, like venous thrombosis.

Genetics Lab Stored Samples

DNA and buffy coat stored on almost all ARIC participants for all visits, with the exception of limited availability of Visit 1 and 2 buffy coat aliquots.

Cryopreserved peripheral blood mononuclear cells (PMBCs) from Visit 5 only.

PAXgene for RNA stored on visit 5 and visit 6 only.

Minnesota Stored Samples—Original Amounts by Type

Visit 1	SERUM – Green 1.5 ml* SERUM – Red 1.1 ml
Visit 2	SERUM – A 1.0 ml SERUM – B 0.75 ml SERUM – C 0.5 ml SERUM – D 0.5 ml Whole Blood (some thawed) 0.6 ml
Visit 4	URINE – 1 aliquot (creatinine) 3 ml* URINE – 1 aliquot (albumin) 3 ml pH 7 adjusted*
Visit 5	EDTA PLASMA (untreated) – 4 aliquots (0.5 mL) CITRATED PLASMA – 4 aliquots (1.0 mL) SERUM – 12 aliquots (0.5 mL) WHOLE BLOOD – 1 aliquot (0.5mL) URINE (pH unadjusted) – 1 aliquot (5 mL) URINE (pH adjusted) – 2 aliquots (5 mL)
Visit 6	EDTA PLASMA (untreated) – 4 aliquots - 3 (0.5 mL) and 1 (1.5mL) SERUM – 2 aliquots (1.5 mL) WHOLE BLOOD – 1 aliquot (0.5mL) URINE (pH unadjusted) – 4 aliquots (1.5 mL)
Visit 7	SERUM – 12 aliquots (0.5 mL) EDTA PLASMA (untreated) – 4 aliquots (0.5 mL) WHOLE BLOOD – 1 aliquot (0.5mL) URINE (pH-unadjusted) – 4 aliquots (1.5 mL)

*If one or more of these vials was not received on a given participant, it is so noted in the inventory management system.

The inventory is managed using the BSI system and includes the following information:

- ID#
- Date received
- Material type, e.g. serum, plasma, urine
- Material modify, e.g. EDTA, sodium citrate
- Original volume at receipt
- Current volume
- Hemolysis if present
- Location in the repository, e.g. freezer, rack, box, position
- If a vial was not received
- Number of thaws
- Tracking for where vials are shipped
- Tracking when vials are returned to inventory

Detailed reports on the inventory can be prepared by request.

*Thawed and refrozen.

Atherosclerosis Lab Stored Samples—Original Amounts by Type

Visit 1	EDTA PLASMA—4 aliquots 1.0 ml
Visit 2	EDTA PLASMA—4 aliquots 1.0 ml
Visit 3	EDTA PLASMA—4 aliquots 1.0 ml
Visit 4	FASTING EDTA PLASMA—4 aliquots 1.0-2.0 ml 2-HOUR OGTT EDTA PLASMA—5 aliquots 1.0 ml
Carotid MRI	EDTA PLASMA (untreated) – 6 aliquots 0.5 ml EDTA PLASMA (BHT) - 8 aliquots 0.5 ml CITRATED PLASMA – 6 aliquots 0.5 ml SERUM – 8 aliquots 0.5 ml URINE (pH unadjusted) – 6 aliquots 5 ml URINE (pH unadjusted) – 1 aliquot 15 ml
Visit 5	EDTA PLASMA (untreated) – 15 aliquots (0.5 mL) EDTA PLASMA (BHT) - 8 aliquots (0.5 mL) CITRATED PLASMA – 3 aliquots (1.0 mL) SERUM – 4 aliquots (0.5 mL) URINE (pH unadjusted) – 2 aliquots (5 mL) URINE (pH adjusted) – 1 aliquot (5 mL)
Visit 6	EDTA PLASMA (untreated) – 15 aliquots – 8 (0.5 ml) and 7 (1.5 mL) EDTA PLASMA (BHT) - 3 aliquots (1.5 ml) SERUM – 4 aliquots (1.5 mL) URINE (pH unadjusted) – 2 aliquots (1.5 mL)
Visit 7	EDTA PLASMA (untreated) – 16 aliquots (0.5 mL) EDTA PLASMA (BHT) - 8 aliquots (0.5 mL) SERUM – 4 aliquots (0.5 mL) URINE (pH unadjusted) – 2 aliquots (1.5 mL)

Hemostasis Lab Stored Samples—Original Amounts by Type

Visit 1	CITRATED PLASMA—6 aliquots 0.5-0.75 ml SERUM—3 aliquots 0.5-0.75 ml FILTERED PLASMA—4 aliquots 0.5-0.75 ml
Visit 2	CITRATED PLASMA—9 aliquots 0.5-0.75 ml FILTERED PLASMA—4 aliquots 0.5-0.75 ml
Visit 3	SERUM—5 aliquots 0.5-0.75 ml FILTERED PLASMA—6 aliquots 0.5-0.75 ml CITRATED PLASMA—9 aliquots 0.5-0.75 ml
Visit 4	CITRATED PLASMA—3 aliquots 0.5-0.75 ml SERUM—5 aliquots 0.5-0.75 ml URINE—1 aliquot 40 ml, pH 7 adjusted

UNC Stored Samples—Original Amounts by Type

Visit 3	RBCs—3 aliquots of 2 mL
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Since most of the biospecimens in the ARIC study are a non-renewable resource, guidelines are used when considering ancillary study requests for precious or limited samples (see separate document on ARIC Sample Distribution Policy, which also has a listing of the number of aliquots still available.)

4.8.2 Use of DNA

With respect of DNA polymorphisms in candidate genes, proposals will need to describe the genetic hypothesis of interest, the specific genes to be typed, and the methods of typing them, the primary dependent variable, endpoint or risk factor of interest, preferred sampling design, and sources of funding. If the identity of the variants is known *a priori*, it should also be included. If the identity of the variants is not known *a priori*, such information should be transmitted to the ARIC coordinating center when it is known. The ARIC study maintains a database of single nucleotide polymorphisms typed (or being typed) on ARIC participants. This database is available on the ARIC website and should be consulted to avoid duplication. When the variant information is known (certainly before data analysis and publication), the information in the table should be conveyed to the coordinating center, as instructed.

Genome-wide and exome-wide arrays and sequencing have been completed on the majority of ARIC study participants. Before requesting use of DNA, consult the ARIC Genetics Laboratory Director, Eric Boerwinkle (Eric.Boerwinkle@uth.tmc.edu; cc Megan.L.Grove@uth.tmc.edu), to check if the variant of interest has already been typed or sequenced and existing data may be made available. Projects proposing use of DNA for methylation studies should also consult the ARIC Genetics Laboratory to determine appropriate visit availability and integration with ongoing projects to reduce batch effects and technical variation.

When a study is approved, the ARIC Coordinating Center has the responsibility of generating a list of ARIC participant IDs to be included and which is consistent with the study's agreed upon

design and objectives. In general, it is better for these ancillary studies to take advantage of case-control, case-cohort, and other contrasts that have already been generated and investigated for other analyses or hypotheses. In addition, preference will be given to proposals focusing on polymorphisms with documented functional significance. When approved by the Steering Committee and requested by the Coordinating Center, the ARIC DNA laboratory will aliquot DNA for the participants into 96-well Matrix racks. The amount of DNA will be determined at the time of ARIC Laboratory Committee approval and will be dependent on the genotyping or sequencing platform. It is suggested that investigators wanting to genotype or sequence genetic variation carry this work out collaboratively with an ARIC Genetics Laboratory. In this way, the work can be carried out quickly and efficiently without wasting DNA and time spent on the aliquoting, shipping and the genotyping and sequencing process. The resulting data would be provided to the investigator along with other ARIC data needed to address the approved hypotheses. There should be no loss of the originating investigator's proprietary ideals or publication rights.

4.8.3 Genomic Data Sharing

Ancillary study investigators are required comply with the NIH Genomic Data Sharing (GDS) Policy (available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html>) to ensure broad and responsible sharing of genomic research data. All ancillary studies proposing genomic research, including but not limited to, genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data, should publicly release these sample-level results via the database of Genotypes and Phenotypes (dbGaP). Data submissions to dbGaP must be routed through and in consultation with the ARIC Coordinating Center. The current dbGaP Data Use Certification Requirements (DUC) allow for posting data derived from ARIC study participants that have provided "Full Consent" and "CVD Research Only" consent. The complete DUC is available at the following link:
https://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?page=DUC&view_pdf&stacc=phs000280.v4.p1.

4.8.4 Use of serum, plasma, and urine

Because ARIC serum, plasma, and urine samples are limited and often stored in large aliquots, policies and procedures have been developed regarding access and use. In general, ARIC contract work, research on already funded ancillary studies, and research supporting the core objectives of the ARIC study (i.e. atherosclerosis, CHD, and heart failure) take precedence with regard to specimen access, especially with regard to incident CVD cases' aliquots. Ancillary study investigators have the obligation to conserve as much biospecimen as possible for future studies. Assays should be multiplexed or done simultaneously when possible and multiple freeze-thaws should be avoided.

The ancillary study proposal form asks for the type and amount of biospecimen being requested. These requests are reviewed by the Laboratory and Steering Committees on a case-by-case basis, and specimen sharing will be decided on the basis of scientific priority, specimen volume, availability and other factors. There is no pre-defined maximum amount, but depleting large volumes (more than 0.25 mL of serum or plasma) and multiple aliquots is discouraged. Justify fully the amount needed.

If the amount approved for an ancillary study matches the amount in the stored aliquot requested, ARIC will provide the full aliquot. If the volume is less, then consideration must be given to how the specimen can best be used. It may be that the whole aliquot will be sent to the ancillary study lab. Then, any remaining sample must be re-aliquoted and returned to the ARIC laboratory providing the sample. Alternatively, ARIC may decide that re-aliquoting the sample may be necessary before sharing it with an ancillary study. In either case, all costs associated with fulfilling an approved request are to be paid for by the ancillary study. This includes sample handling, aliquoting and shipping.

4.8.5 Coverage of ARIC Costs

All costs of the approved ancillary study involving biospecimens are the responsibility of the initiating investigators. Details of any sub-contractual arrangements will need to be made in coordination with NHLBI staff and the participating institutions. Resulting data from the ancillary study must be made available to the ARIC Coordinating Center, as specified above. In this way the value of the ARIC study resource will continue to grow as the foundation database enlarges in size and scope, and analyses can be verified when necessary.

4.9. Industry Participation

Proposals for industry sponsorship or collaboration will be evaluated in accordance with the procedures described above. In addition, as an initial step in study planning, the PI should contact the ARIC Project Officer to determine if a Third-Party Agreement between NHLBI and industry should be developed and implemented or to approve the agreement between industry and the investigator's institution. The NHLBI Third Party Involvement Guideline can be found at <http://www.nhlbi.nih.gov/funding/policies/thirdparty.htm> Based on the contractual mechanism with an industry, the Steering Committee will decide if the study should exclude the participants who gave no consent to data sharing with researchers from private companies.

4.10 Tracking of Contacts with ARIC Participants

Because of the potential of over-burdening ARIC participants with multiple telephone calls and other contacts, ancillary studies must work field centers and the coordinating center to arrange and monitor participant contacts. Specifically, ancillary study investigators must arrange a schedule of contacts with field center coordinators that will prevent too many calls or contacts in close proximity. In addition, the ancillary study must use the coordinating center's data system for tracking phone calls and contacts, so that burden can be tracked

Appendix A

Ancillary Study Proposal Form

Atherosclerosis Risk in Communities (ARIC)

I. Basic Study Information and Projected Impact on ARIC

1. Title of study:
2. Principal investigator(s) (name, address, phone and fax numbers, e-mail address):
3. Collaborators (must include at least one ARIC investigator):
4. Summary of ARIC centers and tasks involved – Leave cell blank if Not Applicable

Center	Enroll or examine participants (N)	Assay samples (N participants)	Provide samples (N participants)	Analyze data (yes/no)
Forsyth Co. Field Center				
Jackson Field Center				
Minnesota Field Center				
Washington Co. Field Center				
DNA Central Lab				
MN Chem Lab				
Lipid Central Lab				
Hemostasis Central Lab				
ECG Reading Center				
Coordinating Center (UNC)				
Other (specify)				

5. ARIC participant and staff involvement:

A. Participants:

Describe number of subjects needed; special characteristics of study population; age and sex distribution. Will participants be contacted, interviewed, examined, or asked to provide specimens? Will the study involve radiation or administration of a drug or contrast? If so, describe participant involvement. Estimate time required of each participant.

B. Stored ARIC specimens:

Describe materials to be used (e.g., stored plasma, urine, DNA). If blood samples are requested, please review the Criteria for Approval section of the Ancillary Study Policy (<https://sites.csc.unc.edu/aric/ancillary-studies-pfg>) in consideration of your description of the following:

Study participants and material requested:

Yes/No	Cohort	Total Number of Specimens	Full Cohort (or →)	Number of Cases	Number of Controls
	All parent study participants (or ↓)				
	Specify sample and specimens in each sample/stratum				

Type of Specimen	N	Volume Requested	Time point (e.g. visit*)	Specify proposed lab and analytes to be assayed at catch lab (be specific)
Serum		ul		
EDTA plasma		ul		
Citrate plasma		ul		
DNA		ug/ng		
Urine		ul		
Other (specify)				

* Please contact the ARIC in advance and indicate here how many tubes of each visit and type you are requesting:

- a. Is the proposed work consistent with the stipulations in the ARIC informed consent form? Yes No (The informed consent forms can be obtained from the collaborating ARIC investigator).
- b. Are thawed/re-frozen acceptable? Yes No

If No, specify reasons for specific assays:

- c. Describe efforts to integrate sample needs with those of other studies to conserve sample and/or limit freeze-thaw cycles.
- d. If approved, when will samples be requested for retrieval?

C. ARIC Field Centers:

Describe effort (and estimated time) required of ARIC staff at each participating center. Include consent, collection of samples, etc.

D. ARIC Coordinating Center:

Describe effort (and estimated time) required of ARIC Coordinating Center staff. Specifically:

** Unless you provide strong justification, the Coordinating Center must be included and its costs budgeted.*

- a. Will the Coordinating Center be involved in data collection, tracking, or preparation of forms or software? or Will these tasks be completed locally by the Ancillary Study, and a data file sent to the Coordinating Center?
- b. If a Reading Center or laboratory is involved, will data be sent directly from the Reading Center or laboratory to the Coordinating Center for processing, or will processing be done locally (either by the Ancillary Study or at the Reading Center/Laboratory)?
- c. Will analyses be done locally by the Ancillary Study or by analysts at the Coordinating Center? If analyses will be done locally, should Coordinating Center verify the analyses?

6. Genomic information (defined as any data from a participant's DNA):

- a. Does your proposal include any genomic materials? (please check one)

No (go to question 7) Yes (see question 6B)

- b. Name the gene(s), genotypes, SNPs to be investigated:

- c. Is genetic information used to address a primary aim or secondary aim of ARIC? (please check one or both)

Primary aim (heart/vascular disease)
 Secondary aim (other health conditions)

List the conditions addressed:

- d. Should DNA-based results be reported to patients' physicians? Base your response on your knowledge of existing literature and current practice regarding increased risk and availability of treatment for adverse outcomes associated with the gene mutations to be studied.

7. Proposed starting and ending dates:

8. Estimated cost by year; number of years:
9. Source of funding; date of submission:
10. Does this study involve the support or collaboration of a for-profit corporation, or do you intend to use the data to patent any process, aspect or outcome of the analysis?
11. What is the advantage, both to ARIC and yourself, of conducting the study within the ARIC cohort versus another population?
12. Impact on ongoing ARIC studies (main study or other Ancillary Studies):
13. Provide the following assurances (answer each):
 - a. Who (name and position) will report progress of the study in the fall of each year? (Ancillary Study PI or designate preferred)
 - b. How will confidentiality of ARIC participants be maintained?
 - c. Data collected by the Ancillary Study, will be provided to the ARIC Coordinating Center for integration into the main database. This will include documentation of newly collected data with labels, and/or laboratory results as well as documentation on methods, visits and units used with specific instructions for using the data in analyses. such as exclusions that were applied. After that has been done the Ancillary Study investigators will receive the integrated file containing data from the main study.

The Ancillary Study PI will be given the first and exclusive opportunity to analyze, present and publish data collected under the auspices of the Ancillary Study. After a reasonable time (in general, 12 months after data cleaning is complete or 12 months after acceptance of primary manuscript, whichever is earlier), Ancillary Study data will be made available for additional uses by other ARIC investigators. It is the responsibility of the Ancillary Study PI to state in writing to the ARIC Steering Committee any special circumstances that would warrant an exception to these guidelines for data sharing. In the spirit of encouraging collaboration, reasonable and justified requests for limiting Steering Committee access to the data will be honored, or a compromise will be worked out.
 - d. Will the Coordinating Center be receiving data from your ancillary study?
 - e. How many papers do you estimate will be written from the Ancillary Study?
 - f. Variables/measurements from the ARIC main study database to be analyzed:
14. If the study will have clinical implications, explain and describe the plan for reporting results to participants and providing recommendations for follow up:

II. Abbreviated Ancillary Study Proposal

Please provide a brief (2 to 4 page) description of the proposed study. Include the following:

Purpose/Aims:

Background:

Hypotheses:

Experimental Design (include sample size justification):

Methods, including:

Participant involvement (if any):

Data to be collected by the ancillary study (attach questionnaires and forms):

Analysis Methods:

Literature References

III. IRB

Select the IRB plan for this ancillary study (either sIRB or Local IRB) and the reason(s) for selection:

sIRB

- a. new data collection at more than one center either directly with ARIC participants or using medical records
- b. lab analysis of ARIC stored samples that use identifiers or require reporting data back to participants
- c. more than one center will see PHI for the study
- d. there eventually may be an FDA application

or

Local IRB

- a. proposals that only use existing ARIC deidentified data (e.g., most student projects, career development projects) will qualify as exempt or non-human subjects research
- b. exclusively single center proposals (this can include some investigators at other sites who are only coauthors or provide services but never see participants or PHI)
- c. lab studies where the ARIC component is already approved in the sIRB parent protocol

Please send the completed form to ARIC-AS@unc.edu and use ‘ARIC ancillary proposal’ in the subject line

For Coordinating Center Use Only

Approved? Yes No

Date:

If approved, ancillary study #

Appendix B

ARIC Ancillary Study Review Criteria

Scoring note: 5 = outstanding, 4 = excellent, 3 = good, 2 = acceptable, 1 = poor, 0 = unacceptable
Passing score ≥ 40

I. Scientific Review -- Scored 0 (lowest) – 5 (highest)	
Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?	
Approach: Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well-reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?	
Innovation: Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?	
Investigator: Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)?	
Environment: Does the scientific environment contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?	
II. ARIC Priorities and Policy -- Scored 0 (lowest) – 5 (highest)	
Potential for contributing to the goals of the ARIC study and the ARIC participant’s commitment to this study	
Draws on unique characteristics of the ARIC	
Efficient use of biologic specimens (consider volume of specimen; number of genotypes/ phenotypes tested; use of high throughput facilities; need for ad hoc thawing)	
Complements the current portfolio of ARIC and its ancillary studies	
Value of the scientific resource contributed to the ARIC	
Years of service to ARIC of the ancillary study principal investigator	
III. Operational Criteria (not scored)	Meets Criterion?
Proposed work and use of biologic specimens are covered by the ARIC informed consent, and meet HIPAA Privacy Rule (if pertinent)?	Y / N / NA
If applicable: is the informed consent accurate, clear and complete; does it appropriately distinguish AS participation from ARIC participation?	Y / N / NA
Notification of study results required? If so, appropriate plan to notify participants in place?	Y / N / NA
If applicable: acceptable burden to ARIC study participants	Y / N / NA
Acceptable burden to ARIC coordinating center / collaborating center(s)	Y / N / NA
Appropriate plan for disposition of stored specimens	Y / N / NA
Appropriate plan for disposition of ancillary study data (e.g., confidentiality, submission of results data to CC)	Y / N / NA

Appendix C
Update on ARIC Ancillary Study
Annual Report Form for _____

Due November 1, _____

Please provide an update on ARIC Ancillary Studies under your direction by answering the questions listed below. The information will be included in the annual report to the Steering Committee and Policy Board.

Email the completed report to: ARIC-AS@unc.edu

Ancillary Study Title: _____

(If your study has used several titles, please give all the titles used, giving the preferred title first.)

Ancillary Study #: _____

(For studies prior to June 1, 2003, this number may need to be completed by the Coordinating Center.)

Current Status:

_____ Not yet started.

_____ In Progress.

_____ Data collection completed.

_____ Publication Stage.

Funding source: NIH AHA Industry Local or other (please specify below)

Funding status / Funded yes no

-If no, plan to resubmit or withdraw?

-If yes, completed? Active? Not started?

Please give comments to explain any conditions that are noteworthy (such as funding not yet received, but expected in next 6 months, funding received and hiring in progress problems encountered, etc)

Please provide a one paragraph summary of your progress and findings, which can be reported to the ARIC Policy Board.

Does this study have a website? yes no If yes, the URL is:

Please answer the following questions:

1. Any change in study status since your last update? (e.g., in data collection, data analysis, manuscript preparation, all activities completed)

2. Was new funding received since your last update? What is the new funding source?

3. What is the status of each publication and presentation derived from the study? Provide full citations for published papers.

- 4a. Did you complete data collection and cleaning more than one year ago or was the primary manuscript accepted more than one year ago?

- 4b. If yes to Q4a, have you sent the data set to the Coordinating center? If so, when?
If not, when do you plan to do so?

A data set containing the important analytic variables should be sent to the Coordinating Center (see the reminder below). Please send the data & documentation separately from this progress report. Data formats such as SPSS, Excel, Stata, and SAS are fine.

5. Have there been any changes in your current mailing address, phone and fax numbers, and e-mail address in the past year? If so, please provide the updated information:

A reminder regarding Publications and Presentations:

You should be aware that any publication or presentation of ARIC Ancillary Study data requires review by the ARIC Publications and Presentations Committee, the Steering Committee, and the NHLBI. All manuscripts must be preceded by an approved manuscript proposal. Abstracts and presentations must be based on an approved manuscript proposal and may not be submitted to any national or international meeting until approved by the above committees.

A reminder regarding Ancillary Study data:

ARIC policy is that data collected by the Ancillary Study, with documentation, should be provided to the ARIC Coordinating Center for integration into the main database. The Ancillary Study PI will be given the first and exclusive opportunity to analyze, present and publish data collected by the Ancillary Study. One year after data cleaning is complete or one year after the primary manuscript has been accepted for publication, whichever comes first, Ancillary Study data will be made available for additional uses by other ARIC investigators. It is the responsibility of the Ancillary Study PI to state in writing to the ARIC Steering Committee any special circumstances that would warrant an exception to these guidelines for data sharing. In the spirit of encouraging collaboration, reasonable and justified requests for limiting Steering Committee access to the data will be honored or some compromise will be worked out.